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DISEASES OF CHILDREN

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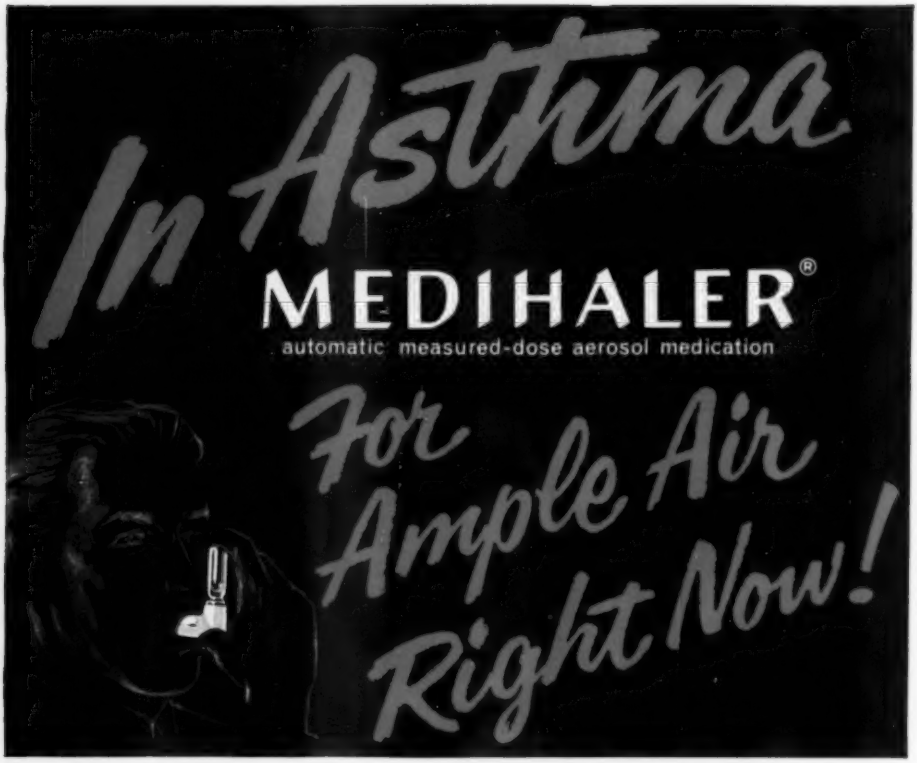

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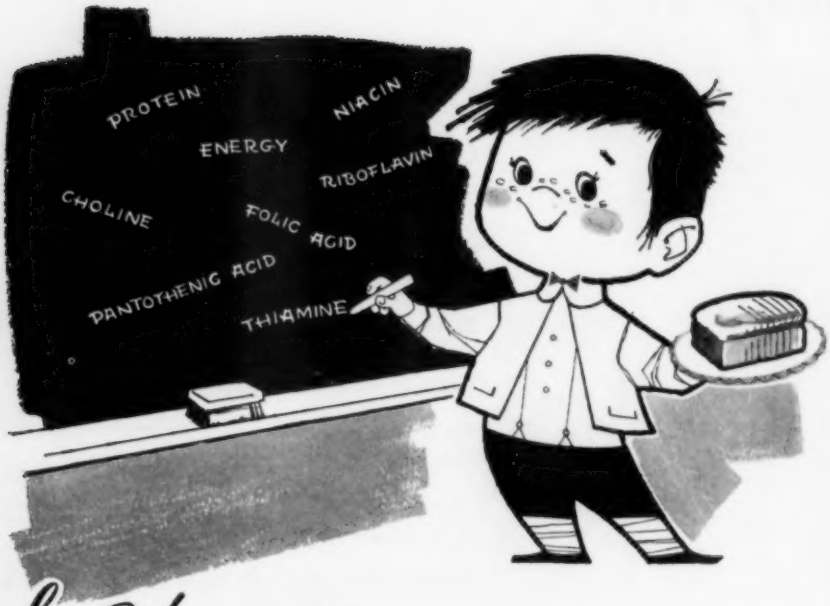

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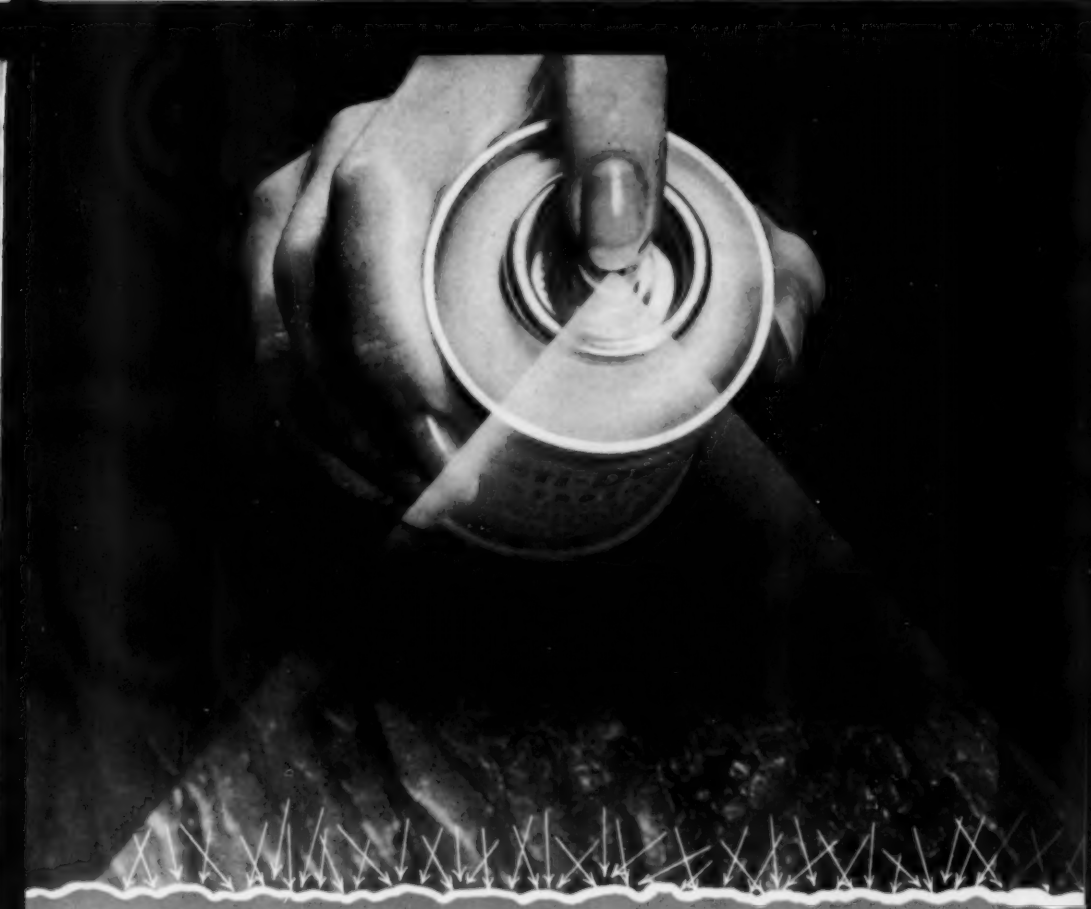

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1. Breslow, L.: Clinical Approach to Infantile Colic. J. Pediat. 50: 196-206, 1957. (Reprint sent on request.)

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Observations on the Potency and Safety of Poliomyelitis Vaccine (Salk Type) Currently Used

KAYO SUNADA, M.D., Salt Lake City; ROBERT K. GERLOFF, M.A., Hamilton, Mont.; DARRELL BROCK, M.P.H.; IONE HOPKEY, R.N., Boise, Idaho; CARL M. EKLUND, M.D., Hamilton, Mont., and ALDON W. KLOTZ, B.A., Boise, Idaho

With the institution, late in 1956, of more stringent methods of safety testing poliomyelitis vaccine, an investigation of the antigenic potency of poliomyelitis vaccine presently available on the commercial market seemed desirable. The present paper presents observations on the antigenic potency of such vaccine, as measured by serologic tests on serums of vaccinated children, and on the safety of vaccine used for this study.

Since this investigation was begun, few reports on the potency of commercially available vaccine have been published. Kelly and Dalldorf [1] observed differences in potency as great as six-hundred-fold between various vaccine lots when antibody response in guinea pigs was used as a criterion of potency. Shaughnessy [2] reported significant differences in antibody response after two injections of various commercial vaccines but found a satisfactory response with all vaccine lots after three injections. Gelfand et al.[3] reported satisfactory results after two injections in children who had preinoculation antibodies to one or more types. Results after two inoculations in children who did not possess previous antibodies were relatively unsatisfactory.

Submitted for publication April 7, 1958.

From the Division of Laboratories, Idaho State Board of Health, Boise, Idaho; U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institute of Allergy and Infectious Disease, Rocky Mountain Laboratory, Hamilton, Mont., and the Communicable Disease Center, Atlanta. Dr. Sunada's present address: Department of Pediatrics, University of Utah Medical School.

Methods of Study

1. *General Procedure.*—Children residing in three areas of Idaho, widely separated geographically, were chosen for this study. Among 748 included in the investigation, 605 were given vaccine and 143 uninoculated children were considered control subjects. The ages of these children varied from 5 through 15 years. Nearly equal proportions of boys and girls were included. All of the children except two (oriental) were of white parentage. None had previously received any injections of poliomyelitis vaccine.

The study was conducted from March, 1956, through May, 1957. Each child received three 1 ml. doses of vaccine given intramuscularly into the left arm. The first two injections were given during spring and early summer of 1956. The second injection was given one month after the first, and the third, seven months after the second. Children were potentially exposed during a poliomyelitis season between the second and third injections, when 110 cases of poliomyelitis were reported among a population of 650,000. Type 1 poliovirus was the predominant cause of disease.

The poliomyelitis vaccine used in this study was produced by a single manufacturer. For the first two injections, a single lot was used. Another lot was necessary for the third injection, since poliomyelitis vaccine becomes outdated in six months. For this last injection, a separate lot was used in each of the study areas.

In addition to safety and potency tests performed by the manufacturer and by the Division of Biologic Standards, National Institutes of Health, the lot of vaccine used for the first and second injections was tested for live poliovirus by Dr. J. T. Syverton, University of Minnesota. His test included inoculation of aliquots of vaccine into cultures of HeLa cells and into monkeys that had been treated with cortisone and x-ray. In an indirect test, conducted by the Idaho State Health Department, stool samples were collected for virus isolation from vaccinated persons after the first injection of vaccine, and from unvaccinated children.

Continuous epidemiological and clinical observations of vaccinated children were maintained. Careful inquiry was made concerning illness in each child after every injection of vaccine. Particular attention was given to the occurrence of local reactions, illness of a general nature, and possible allergic reactions. Comparable histories of illness also were obtained from the control group. Histories were taken to detect any illness in families after vaccination of children. School attendance records were examined to compare the rate of absenteeism in the two groups after vaccination. Finally, all reported cases of poliomyelitis in the state were noted and those occurring in the study area were investigated epidemiologically to determine any association with vaccinated children.

2. *Laboratory Procedure.*—Blood specimens were collected from children before vaccination, one month after the first dose of vaccine, just prior to administration of the third dose, and, the last specimen, one month later. Because all children were not available for clinics at which blood samples were collected, the total number of serums obtained at each bleeding varied. Sera were separated from blood clots at the Idaho State Health Department Laboratory in Boise and were frozen until shipped to the Rocky Mountain Laboratory, Hamilton, Mont., where they were kept frozen at —24 C until tested.

Antibody response was measured by a metabolic inhibition type of neutralization test which embodied features of two tests previously described by Salk et al.[4] and Melnick et al.[5] Trypsinized monkey kidney cells were prepared by a method similar to the one described by Rappaport.[6] The highest dilution of serum which sufficiently protected monkey kidney cells against 100 to 300 TCD_{50} (50% infectious for tissue culture) doses of virus so that pH decreased to 7.0 or below was considered the antibody titer of that serum. All tests were performed in cups of disposable plastic panels sterilized by ultraviolet irradiation. Nutrient fluid consisted of Hanks' balanced salt solution containing 0.5% lactalbumin hydrolysate and 2% horse serum. The mixture of serum, virus, cells, and nutrient fluid in each cup of the panel was overlaid with an equal quantity of mineral oil. Each panel was then covered with a sheet of sterile aluminum foil and incubated at 36 C for 10 to 12 days, the exact interval being determined by the behavior of the controls.

Each test was accompanied by suitable controls, including virus and cell titrations, plus controls on serum toxicity, virus dilution, cell dilution, and media. In addition, aliquots of a single serum pool of known antibody content were included in every test for further control on standarization of conditions between tests on various dates. All sera were routinely tested in dilutions of 1:8, 1:16, 1:32, 1:64, 1:256, and 1:1024. Titers of 1:8 or greater were considered significant.

Stool specimens were collected from 161 vaccinated children in two areas on the 13th, 14th, and 15th days after they had had the first inoculation of polio vaccine. At the same time, stool specimens were collected from 50 unvaccinated children residing in these same areas.

Each stool specimen was emulsified in a sterile mortar with buffered saline and then centrifuged under refrigeration at 12,800 g for 30 minutes. The supernate was removed with a sterile capillary pipette and held at —50 C until inoculated onto tissue culture. One hundred seventy-one specimens were tested in monkey kidney tissue culture, and forty specimens were tested in KB (Eagle) cells. Maintenance medium was changed on the third and sixth days after inoculation. Fluids from cultures showing cytopathogenic effects were passed once, and viral isolates were then typed. Tissue cultures which remained normal after a 10-day incubation period were discarded.

Results

1. *Lack of Evidence of Live Virus in the Vaccine.*—Injection of lots of vaccine used in this study was not accompanied by any illness suggestive of poliomyelitis in either the vaccinated children or their contacts. Tests by Dr. Syverton, which involved inoculation of both tissue culture and monkeys, did not detect live poliovirus in the lot of vaccine used for the first two injections. Following the first injection, Type 3 poliovirus was isolated from stool specimens from 2 of 121 vaccinated children in one of the areas. However, these specimens were collected at a time when Type 3 poliovirus was known to have caused disease in this area. Virus was not

TABLE 1.—*Effect of Prevaccination Polio Antibody on the Response of Children to Vaccination*

Prevaccination Antibody Types Present	Percentages of Children Developing Antibodies After Vaccination								
	Type 1			Type 2			Type 3		
	1st *	2d	3d	1st	2d	3d	1st	2d	3d
None	3 (3/104) †	7 (6/90)	73 (60/82)	20 (21/104)	49 (44/90)	99 (81/82)	2 (2/104)	4 (4/90)	29 (24/82)
Type 1	—	—	—	94 (68/72)	92 (48/52)	100 (43/43)	13 (9/72)	10 (5/52)	51 (22/43)
Type 2	89 (40/45)	96 (23/24)	100 (24/24)	—	—	—	22 (10/45)	29 (7/24)	67 (16/24)
Type 3	7 (5/75)	13 (8/60)	89 (42/47)	72 (54/75)	77 (46/60)	100 (47/47)	—	—	—
Types 1 & 2	—	—	—	—	—	—	50 (18/36)	33 (7/22)	86 (12/14)
Types 2 & 3	80 (30/49)	100 (12/12)	100 (7/7)	—	—	—	—	—	—
Types 1 & 3	—	—	—	94 (82/87)	100 (6/6)	No specs.	—	—	—
Total	57/273	49/186	133/160	225/338	144/208	171/172	39/257	23/188	74/163

* 1st, 2d, and 3d refer to serums collected after the first, second, and third doses of vaccine.
† Fractions in parentheses indicate numbers of children on whom percentages are based.

isolated from 40 vaccinated children in another area or from 50 control children in both areas.

2. *Antibody Response.—(a)* Control Children: A second blood specimen was collected from 86 children in the control group. Natural infection during the month interval between the first and second bleedings was evident in only one child, whose antibody titer increased from less than 1:8 to 1:64. Continued study of the control children after the second bleeding was impossible, because many of them requested vaccination thereafter.

(b) Children with Poliovirus Antibody in the Prevaccination Blood Specimen: When Type 1 antibody alone was present in the preinjection serum, Type 2 antibody appeared in 94% of the children after the first dose of vaccine (Table 1). The response was similar when only Type 3 antibody was present initially, and resulted in 72% conversion for Type 2. When antibody against Types 1 and 2 was present, Type 3 antibody appeared in a higher percentage of children (50%) than when Types 1 and 2 were present singly (13% to 22%). These differences were still evident after three inoculations (86% as compared with 51% to 67%). When antibody of Types 1 and 3 or 2 and 3 was present in the prevaccination blood serum, all three types of antibody generally appeared after only one injection of vaccine.

(c) Children Without Poliovirus Antibody Before Vaccination: After one dose of vaccine, the antibody response in children having had no previous exposure to polioviruses, as indicated by absence of poliomyelitis antibody in their prevaccination blood sera (Table 1, Line 1), was predominantly Type 2 (20%); that of Types 1 and 3 was only minimal, 3% and 2%, respectively. After the second inoculation, response of Types 1 and 3 antibody was still poor, 7% and 4%, respectively; for Type 2 it had risen to 49%. After three inoculations, 73% and 29% of the children showed Types 1 and 3 antibody, respectively, and practically all (99%) had Type 2 antibody. Table 2 presents a more detailed analysis regarding the 82 children who were followed through the entire study; i. e., they were given three doses of vaccine and submitted to all four bleedings.

Whereas Type 2 antibody resulting from natural exposure to the virus had a marked influence on development of heterotype antibody following vaccination, Type 2 antibody resulting solely from vaccination did not exert a definitely demonstrable influence. This fact is partially revealed by Tables 1 and 2 but is seen more clearly in Table 3, which, for ease of comparison, focuses on two specific groups of children

TABLE 2.—*Antibody Response in Eighty-Two Children Seronegative Against Poliovirus Before Vaccination*

	Children Developing Indicated Antibody Spectra								
	0-0-0 *	+-0-0	0-+-0	0-0-+	+-+-0	0-+-+	+-0-+	+-+-+	Total
After 1st inoculation	65	0	12	0	3	2	0	0	82
After 2d inoculation	38	1	32	0	5	3	0	3	82
After 3d inoculation	1	0	21	0	36	0	0	24	82

* 0-0-0 indicates complete absence of polio antibody; +-0-0 indicates Type 1 antibody only, etc.

in the first two tables. Group 1 represents the 12 children (taken from Table 2, Line 1), who were originally "triple negative" and who developed only Type 2 antibody (0-+-0 spectrum) after the first dose of vaccine. Except for variations in antibody titer, they were then serologically comparable to Group 2 (taken from Table 1, Line 3) which consisted of 45 children possessing the 0-+-0 antibody spectrum before vaccination. A second dose administered to Group 1 revealed a distinct immunologic difference, however, since this group failed to develop heterotype antibody. In contrast, Group 2 children developed such antibody after the first dose, especially against Type 1.

After a second dose of vaccine had been given to the originally "triple negative" children, 32 of 82 had developed the 0-+-0 antibody spectrum. Incidence of heterotype antibody in the group was still low. After a third dose, Types 1 and 3 antibody did develop to a much greater extent, but the likelihood of development was not appreciably affected by previous occurrence of vaccine-induced Type 2 antibody (Table 4). The differences in heterotypic response which did occur in children possessing Type 2 antibody as compared with those lacking it probably reflect not a true cross antigenic effect but instead a difference in the innate ability of persons to produce antibody. The children who still had not responded to the Type 2 component, a relatively good antigen, after two injections of it would be considered poor antibody producers and would also not be expected to respond as well to the Types 1 and 3 components, following a third injection. In general, the data obtained indicate that the three components of the vaccine acted as specific entities and have little antigenic relationship to one another. Final development of antibody to any one type resulted from a cumulative effect of that type of antigen rather than from a cross effect between types. An experiment using the three antigens singly would be necessary to show definitely whether or not there is any sharing of antigens by the three virus types.

As an adjunct to the main part of the study, heretofore described, a fourth dose of vaccine was given to 39 children who still lacked one or more types of antibody after the customary three-dose course. The extra inoculation was given approximately three months after the preceding one. Twelve of these children had possessed

TABLE 3.—*Compartive Effect of Vaccine-Induced and Naturally Acquired Type 2 Antibody on Subsequent Antibody Response*

	Children Positive for the 3 Antibody Types					
	Group 1 *			Group 2 †		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Before vaccination	0	0	0	0	45	0
After 1st dose of vaccine	0	12	0	40	45	10
After 2d dose of vaccine	0	12	0	—	—	—

* Twelve children initially "triple negative" but developing Type 2 antibody after one dose of vaccine.
† Forty-five children possessing Type 2 antibody initially.

TABLE 4.—*Subsequent Development of Type 1 and Type 3 Poliomyelitis Antibody in Children in Whom Vaccine-Induced Type 2 Antibody Was Either Present or Absent*

Children,* No.	Antibody Spectrum After 2 Doses of Vaccine	Per Cent Positive for Heterotype Antibody After 3d Dose of Vaccine	
		Type 1	Type 3
32	0-+-0	78	31
38	0-0-0	60	16

* Children in both groups were "triple negative" before vaccination.

TABLE 5.—*Distribution of Antibody Titers in Twenty-Seven Children After Four Doses of Poliomyelitis Vaccine*

Poliovirus Type	Children * Who Attained the Indicated Antibody Titer (Expressed as Reciprocal), No.								
	< 8	8	16	32	64	128	256	512	1024
1	4	4	5	5	4	2	0	2	1
2	0	1	0	1	3	12	6	3	1
3	12	6	4	3	1	0	1	0	0

* All children were "triple negative" before vaccination and still lacked antibody against one or more types of poliovirus after three doses of vaccine.

antibody against one type of virus prior to the first injection of vaccine. All became "triple positive" following the fourth dose, except one child who still lacked Type 3 antibody. Of the remaining 27 children, who had been "triple negative" prior to vaccination, 85%, 100%, and 56% possessed Types 1, 2, and 3 antibody, respectively, after the fourth dose. Final sera from them were tested in all twofold dilutions from 1:8 through 1:1024. Levels of Type 3 antibody were generally low, more so than in children who had responded to earlier doses of vaccine (Table 5).

Comment

In this study the antibody response following the use of vaccine in children with previously occurring polio antibody corresponds with that already reported by Salk[7] and Francis.[8] Type 1 antibody development was influenced significantly by previous exposure of a person to Type 2 virus, and Type 2 antibody development was similarly influenced by previous exposure to either Type 1 or Type 3 virus. On the other hand, Type 3 antibody response was little influenced by previous exposure to Type 1 or Type 2 virus, unless there had been exposure to both of them.

A definite relationship between the virus types could not be demonstrated when vaccine was used in children who had not been previously exposed to poliovirus, as manifested by the absence of antibodies. The antibody response following vaccination appeared to be more type-specific than that following natural infection. In the preparation of the particular lots of vaccine used in this study, antigenic components shared by the respective virus types apparently were sufficiently reduced in amount so that they did not stimulate definitely detectable antibody production in a person not previously exposed to polioviruses.

The present findings, that the Type 2 component of the vaccine was most antigenic and the Type 3 component was a poor antigen, conform to the experience of Gelfand and associates.[3] Their observation that initial Type 1 antibody influenced the appearance of Type 3 antibody could not be confirmed.

The observations of Shaughnessy[2] on "triple negative" children, which indicated poor antibody response after two inoculations of vaccine but greatly increased response after three, were confirmed with regard to Types 1 and 2 antibody. However, our observations did not confirm those of Shaughnessy with respect to Type 3, since at least one more inoculation was needed to effect a similar response.

The present investigation indicates that antibody response of children having any one type of polio antibody prior to vaccination affords a very poor measure of the potency of a vaccine lot, because of cross relationships between poliovirus types. A weak antigen can cause an antibody response in such children, whereas none would occur in children lacking previous exposure to poliovirus. Potency of vaccine lots should, therefore, be measured in "triple negative" children and not in the general child population.

Summary

Three inoculations of poliomyelitis vaccine, produced by one manufacturer, were given according to the schedule recommended by Salk. Use of these vaccine lots was not accompanied by any illness suggestive of poliomyelitis in either vaccinated children or their contacts. Direct tests of one of the vaccine lots by an independent

investigator gave no evidence of live virus. In children lacking polio antibody prior to vaccination, Type 1 antibody appeared in 73%; Type 2 antibody, in 99%, and Type 3 antibody, in 29%, following three doses of vaccine. After a fourth dose of vaccine, given to a portion of these children, the percentages increased to 85%, 100%, and 56%, respectively. Antibody response after the first and second inoculations was especially poor for the Type 1 and 3 components and only fair for the Type 2 component.

The antibody response in children with varying type combinations of prevaccination antibody was good, in most instances, after three inoculations of vaccine. However, among children possessing Type 1 antibody alone before vaccination only 51% developed Type 3 antibody.

The relationships between Types 1 and 2 virus and between Types 2 and 3, previously mentioned by Salk, were confirmed where antibody from natural infection was present at the time of vaccination, but these relationships could not be clearly demonstrated in children lacking this initial antibody.

Evidence is presented which indicates that the antigenicity of poliomyelitis vaccine should be measured in children who do not possess antibody resulting from natural exposure to poliovirus.

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Early Diagnostic Criteria of Congenital Hypothyroidism

A Comprehensive Study of Forty-Nine Cretins

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It seems clearly evident that the earlier the diagnosis of congenital hypothyroidism is established and adequate therapy is begun the more satisfactory is the prognosis. In a series of 49 cretinous patients seen at the University Hospital the average age at the time of diagnosis was 12 months. We believe that in most of these cases a diagnosis could have been made before 6 months of age. A survey of these patients revealed that 54% had at least three prominent symptoms of their disease by the end of the first month of life and 75%, by the end of the third month. At present there are generally available laboratory studies that can confirm a suspicion of congenital hypothyroidism in better than 90% of cases. Most of the pediatric textbooks and more extensive reference works pay little attention to the early time of appearance of the several important, though nonspecific symptoms and, in describing the typical cretin, fail to emphasize that many of the classical physical findings are relatively late in onset. The present detailed study was made in an attempt to define more precisely criteria that will lead to an earlier recognition of the condition.

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Patient Material and Methods

All of the 49 patients included in this survey have been followed in the University Hospital from 1 to over 30 years. Thirty-one of the patients were seen by us within the past year as part of a study which included a carefully obtained interval history in addition to a reevaluation of the original history. Both parents, when alive, were interviewed. A genetic evaluation was done by a member of the Department of Human Genetics of the University Medical School. Psychometric tests were obtained on all of the patients and will constitute a portion of another report. Special studies were carried out in most of the family groups, including protein-bound iodine determinations,[1] radioactive iodine uptake by the thyroid at 1, 2, and 24 hours,[2] paper chromatography of serum butanol-extractable iodine compounds,[3] serum cholesterol determinations,[4] and determinations of basal metabolic rate in the parents and older children.

The hospital records of the 18 patients who were not seen as a part of the special study were reviewed, and a detailed questionnaire was sent to the families.

The age range of the patients at the time of preparation of this report was from 12 months to 32 years. All were of the white race, and 37 of the infants were born in Michigan, 3 were born outside of Michigan, and for 9 the place of birth was not known.

Summary of the Data

Early Infancy.—A very detailed history was obtained from the parents in an attempt to evaluate the first signs or symptoms of thyroid deficiency. Every effort was made to acquire accurate information and to eliminate the possibility of the parents giving erroneous dates of the onset of observed abnormalities. As a means of comparison, 100 normal infants who had been followed in the University Hospital well-baby clinic for at least six months were

TABLE 1.—*Symptoms in Hypothyroidism*

Symptom	49 Cretins, %*	100 Normal Infants, %*
Lethargy	98	0
Constipation	92	2
Feeding problems or failure to gain	83	5
Respiratory problems	76	6
Dry skin	76	1
Thick tongue	67	0
Hoarse voice or cry	67	0
Umbilical hernia	67	8
Prolonged icterus neonatorum	12	0
Goiter	8	0

* The percentage figures indicate a positive response obtained in the history or noted by parents during the first six months of life in the 49 cretins studied and the 100 infants chosen at random from the university hospital well-baby clinic.

studied. Table 1 shows the results of this comparison.

"Lethargy" was a term seldom used by parents, but it has been chosen as an inclusive term indicating physical and mental torpor. This symptom complex constituted a part of the chief complaint in nearly two-thirds of the initial histories and in this group was noted before the end of the third month of life. In some the somnolence was a part of the feeding problem, as will be noted later. Mothers would make such statements as, "She was unusually quiet and never moved much," "She almost never cried," or, as one said, "She was the best baby I ever had." Lack of interest in the environment was very common, but true retardation of motor development was seldom noted until several months after the initial observation of lethargy.

Sluggishness of intestinal peristalsis was a quickly recognized characteristic of the hypothyroid patient. Only four of our cretins did not manifest this difficulty. The constipation was persistent and often resistant to the usual methods of treatment. Approximately one-third of the cretins had some difficulty in bowel movements during the first month, and slightly over two-thirds, by the third month of life. Typical quotations from the interviews with parents were, "She only had two bowel movements a week and she had a hard time having those," ". . . almost never had a bowel movement without an enema," and "The stools were always hard and dry and we used all sorts of cathartics." In two instances the infants were alleged never to have had spontaneous defecation from the age of 1 week until thyroid therapy was started at 6 and 12 months, respectively.

During the first month of life difficulty in feeding was noted by more than half of the mothers of the congenitally hypothyroid infants. This problem and failure to gain weight constituted the commonest chief complaints in our series during the first six months of life. In most instances the child was slow in nursing, often requiring an hour or more to drink 2 or 3 oz. of formula. It was very typical for the mother to relate many visits to physicians with frequent changes in formulas or in nursing techniques resulting in no improvement in feeding habits. Lack of enthusiasm for food was related in part to the general somnolence of the infants. The large tongue was another factor interfering with sucking and swallowing. Breathing difficulties also augmented this problem. Vomiting was a prominent symptom in only one case.

Respiratory distress associated with cyanosis appeared in 15 cases in the first months of life. Six of the parents reported cyanosis at some time during the first 24 hours after delivery, and in three cases oxygen was administered to the cretin for longer than one day. After the immediate neonatal period the cyanotic attacks were nearly always associated with feeding and choking. Five of the mothers gave the opinion that the large tongue so interfered with sucking and swallowing that it caused the choking. One infant was asphyxiated at the age of 10 weeks, with autopsy finding of marked myxedematous changes of the tongue, epiglottis, and larynx and aspiration of formula. Noisy respiration was a common complaint, and several of the infants were stated to have had "nose colds" or "stuffy noses" since birth.

Abnormal dryness of the skin was noted within the first month by one-third of the parents and within the fourth month of life by more than three-fourths. An often-repeated observation was that baby oils and

creams gave either no relief or only temporary aid. Less frequently other changes in the skin were noted, including pallor in 10, mottling and "coldness" in 8, and carotenemia ("yellow skin") in four. In six patients prolonged icterus neonatorum was observed lasting for "several weeks." One mother stated that her child remained "jaundiced" for a year, but no laboratory studies were available, and it could not be ascertained whether this was icterus or carotenemia. Typically myxedematous changes of the skin and subcutaneous structures were not recognized by most of the parents until after the third or fourth month and even then, by many parents, only in retrospect, after therapy induced the regression of these findings.

Thickening of the tongue to the point that it protruded from the mouth and interfered with feeding or respiration was noted by history in two-thirds of the series and was the chief complaint in several. This abnormality was usually observed by the beginning of the third month and always by the fifth month. Five of the mothers had observed the enlarged tongue early in the neonatal period. In several instances physicians had reassured the mothers that there was nothing to be concerned about.

Umbilical hernia was noted during the first week of life in two-thirds of the series. It seldom developed later.

Four (8%) of the patients were observed to have goiters either at birth or in early childhood. In two the enlargement of the gland was relatively small, and in two the enlargement was considered gross. In view of the recent interest in cretinism being due to an inborn defect in the synthesis of thyroid hormone (Stanbury[5] and Wilkins[6]), these four patients were given radioactive iodine (I^{131}) tracer studies after withdrawal of all medication. In three there was an initial rapid uptake of the iodine within 5 hours by the goitrous gland and then a rapid elimination within 24 hours of the administered dose. This suggests ability of the gland to take up iodine but an inability to synthesize the hormone. Paper chromatography studies of serum butanol-extractable iodine compounds on two of these patients showed only large amounts of iodide and mono- and diiodothyronine and minimal quantities of thyroxin. The fourth patient had a low uptake of I^{131} at 2, 4, and 24 hours.

Early Diagnostic Signs.—The early diagnostic signs that can be observed by the physician before the classical picture of the myxedematous cretin becomes apparent will be discussed as presented by the 20 patients in this series in whom diagnosis was made before the age of 5 months (Table 2).

Not one of the infants had attained an expected or normal linear growth for his chronologic age in comparison with tables of Stuart and Meredith[8]; 60% were below the 3d percentile range, and all were well below the 10th percentile figures. There was a less marked deviation in weight from the normal; only 40% were below the 3d percentile figure for their ages and 20% fell above the 10th percentile range. It is of interest to note that all of the patients in which diagnosis and therapy were not begun until after 7 months of age had markedly retarded height and weight measurements.

Although lethargy is somewhat difficult to evaluate in a brief examination, it is pertinent to remark that this was stated to be present at the time of the initial observa-

TABLE 2.—*Physical Findings* *

Findings on Physical Examination	Per Cent Positive
Umbilical hernia	70
Lethargy	70
Retarded linear growth	60
Hypothermia	55
Respiratory embarrassment	50
Dry skin	50
Early myxedema	50
Bradycardia	35
Large tongue	30
Carotenemia	30
Goiter	8

* The positive findings upon physical examination of 20 congenitally hypothyroid infants whose disease was diagnosed before the fifth month of age. See text for further amplification of this Table.

tion in 70% of the physical examinations and later in all patients after hospitalization and more prolonged observation were possible. Complete lack of response or minimal response to usual stimuli was characteristic. This finding was usually a simple confirmation of a parent's complaint.

Dry skin was noted in half of the infants and was frequently associated with signs of poor circulation, such as mottling, acrocyanosis, coolness, and pallor. Carotene staining of the skin was observed in six (30%), often when this had not been noticed by parents. None of the patients had icterus when first seen by us. Half of the infants had evidence of myxedema at this early age, with puffiness around the eyes, thickened lips, and generally coarsened features. One at 5 weeks of age had already developed considerable myxedema of the face, neck, and shoulder girdle.

A definitely large and protruding tongue was present in six (30%) and doubtful in an equal number, according to the first examiner. A hoarse or deep cry was noted in half of the cases and was either not remarked upon or was absent in the others. Loud or difficult breathing with partial nasal obstruction was present in a like number of the cretins diagnosed before the fifth month.

The heart rate in 35% of the patients was 100 or below, which probably can be interpreted as a true bradycardia at this age. It should be emphasized, however, that there is considerable normal variation and that several readings need to be taken for accurate evaluation. Similarly with hypothermia, the results may be difficult to properly interpret, but in 11 (55%) rectal temperature persisted below 98.0 F (36.6 C) until therapy was started. One cretin, 6 weeks of age, was referred by a physician who had observed no temperature above 96.5 F and had kept the infant in an incubator regulated at an average of 82 F throughout the entire six weeks. This patient had already developed considerable myxedema and other signs of hypothyroidism.

Other findings are given in Table 2 and need little comment. We again wish to emphasize that these were early findings in a group of patients whose disease was diagnosed by the end of the fourth month of life.

Prenatal and Birth History.—Age of mothers at birth of the cretin was from 16.5 years, to 45 years, with an average of 26.9 years. Average age of the fathers was 27.3 years.

The order of birth of the cretin child in 36 of the families was as follows:

	Cases, No.
1st child	17
2nd child	9
3rd child	5
4th child	2
5th child	2
6th child	1

Five of the mothers, of 33 instances in which the information was available, had had one or more spontaneous abortions before the birth of the affected infant. One mother had a spontaneous abortion in the first pregnancy following the birth of the cretin. Twenty-four families had one or more normal children following the birth of the cretinous child.

There was an incidence of 15% for congenital anomalies other than those of the thyroid gland in 31 families carefully screened for genetic factors. These included only siblings, parents, grandparents, aunts, and uncles. No congenital anomaly showed unusual predominance, nor was any obvious pattern present.

The number of siblings in the families averaged 2.96, with a maximum of 9. In 39 families all but five of the siblings were alive at the time of the study.

Pregnancy was uneventful in most of the mothers. In the 39 families where reliable information was obtained there had been no history of toxemia or unusual medication except for one mother who required thyroid in relatively large doses.

This family will be described in more detail subsequently. Two mothers had mild hypertension during part of the pregnancy. Four of the mothers estimated that their pregnancies lasted over nine months, but only one of the infants weighed more than 9 lb. One threatened abortion with scanty bleeding occurred at seven months, but full-term gestation was completed after one month of bed rest and there were no further complications. There were no premature babies, if only estimated time of gestation was considered.

Delivery was uncomplicated in 42 of 46 patients. There were three breech deliveries and one prolonged labor of 42 hours.

Thirty-six of the forty-nine cretinous children were female, following the pattern of thyroid disease in general. The significance of this predominance of the female sex remains unexplained.

The average birth weight of 45 of the cretinous infants was 8.0 lb. (3630 gm.), with the smallest weighing 4.0 lb. and the largest, 11.0 lb. Three of the infants were over 9 lb. (4090 gm.), and six were under 6.5 lb. (3000 gm.).

History of Thyroid Disease in the Family.—Four families had siblings with cretinism. Seven of these children are included in the case material of this report. One died at a very early age in another hospital. The affected siblings in each family were of the same sex, four males and four females.

One mother was severely hypothyroid and became pregnant only when taking thyroid. At the time of her study, in 1957, approximately two years after parturition of the second of two cretins, her physical examination was compatible with mild myxedema. She had received no medication for a period of six weeks. Her basal metabolic rate was −32%; I^{131} uptake of the thyroid at 24 hours was 0.45%, and the scintiscanner showed that no thyroid tissue was present in the neck. Her only two children were cretins. Of 36 families, 11 (30%) gave a positive history of thyroid disease. Four cretins had a cretinous sibling, as previously noted. Seven had a history of goiter in a parent, sibling, or grandparent. Two of four goitrous cretins had other members of the family with goiters, but the goiters were apparently not associated with hypofunction. These were included in the seven families. One sibling died in early childhood as a result of surgical removal of the "goiter," and the nature of this abnormality was not known. Most of the goiters were of the colloid or colloid-adenomatous type. In four additional families there was a history of thyroid abnormality in an uncle, aunt, or first cousin.

Four of the mothers took some thyroid during their pregnancy, but, with the exception of the one mother whose history is given above, this was taken in a somewhat haphazard way and none were receiving this medication in a consistent manner.

With the exceptions noted above, physical examination and laboratory tests carried out on the parents and siblings of 31 cretins failed to reveal any physiologic abnormality of thyroid function.

Laboratory Findings at Time of Diagnosis.—Fifteen of the patients had protein-bound iodine determinations before therapy, and all results were lower than normal (3.4μg. to 7.0μg. %), with a range from 0.42μg. to 2.72μg. %. The youngest had a serum protein-bound iodine value at 5 weeks of age of 1.6μg. %, and this was one of the infants with the severest clinical picture. The highest value was obtained in an infant 2 months old. At 10 years of age, when this child returned for the special study, it was demonstrated that she did have some thyroid tissue, with a rapid uptake of I^{131} of 19% at two hours but a subsequent fall to 1.8% at 24 hours. Similar I^{131} uptakes were demonstrated in three additional patients, three of the four having goiters and the other one, a barely palpable thyroid gland. As previously stated, one patient with a goiter had a low uptake of I^{131} at 2, 4, and 24 hours. In

all of these patients medication had been withheld for at least six weeks prior to these studies.

Seventeen of the patients without demonstrable goiters had I^{131} uptakes prior to thyroid therapy. All of these patients had low uptakes at 2, 4, and 24 hours. Some of these patients were included in an original report by two of us (G. H. L. and W. H. B.).[9]

Two patients did have uptakes below normal but sufficiently high at 24 hours (13% and 14%) to demonstrate some evidence of thyroid tissue. These two were brothers and were products of the pregnancies from an athyroid mother. This family will be discussed in greater detail in a subsequent report.[10] The range in these 17 patients was from 0.0% to 14% in the 24-hour test. One patient with a large goiter had an uptake of 16.0% at two hours and 16.0% at 24 hours. Her protein-bound iodine was 1.5μg. %, and, unfortunately, paper chromatography studies were refused by the parents.

Alkaline phosphatase was determined in the blood of 11 patients and was below 6.5 Bodansky units (B. U.) in all but one (normal, 7 to 10 B. U. in our laboratory). The youngest patient was 2 months old and the oldest was 48 months old.

Blood cholesterol determinations were carried out in 42 of the 49 patients. Seventeen of these patients were under 6 months of age, and only three had values above the normal range of 250 mg. %. After one year of age the cholesterol level was significantly elevated in the majority of untreated cretins.

Routine blood cell counts were done on the majority of the patients. The only pertinent finding was anemia in approximately one-half of them. In general, this was the picture of an iron-deficiency anemia with a hemoglobin determination relatively lower than the depression of the red blood cells. In a very small per cent the peripheral blood picture resembled that of a moderate hypoplastic anemia, with a depression of hemoglobin, red cells, and reticulocytes. Anemia was considered to be present when the hemoglobin value was less than 9.8 gm. The lowest value was 6.5 gm., in a 4-year-old cretin.

Radiologic examination of the bones was carried out in all but four of the total number of patients. In eight of these the part of the skeleton chosen for examination was unsatisfactory to adequately evaluate bone development. In every one of the remaining 37 cretins there was some delay in osseous maturation. In the first four months of life the distal femoral epiphysis and the foot were examined., Beyond this age the wrist was the most useful area in which to obtain films; however, other areas were sometimes used, depending upon the patient's chronologic age. Without exception, the longer adequate therapy was delayed the more marked was the relative retardation of bone maturation. Several standards were used, especially those of Greulich and Pyle,[11] Christie,[12] and Watson and Lowrey.[13] A total of 10 patients were followed for examination of linear bone growth, as suggested by Wooley and McCammon.[14] All of these were 6 months or less in age at the time of diagnosis and were below the 2 S. D. (standard deviation) criterion set by these authors for the length of the radius as examined by the technique of a teleoroentgenogram.

Epiphyseal dysgenesis, as described by Wilkins,[15] was present at the initial examination in only 15% of the cretins. However, as soon as therapy was begun and ossification of cartilage took place, the majority of follow-up films did show the irregular deposits of calcium.

Electrocardiograms were obtained prior to therapy in seven patients. Bradycardia was present in four, and low voltage was described in five. One patient had an incomplete bundle branch block. Two were considered to show no definite abnormality for the age of the child.

Later Laboratory Studies.—Of the 31 patients who returned for the special stud-

ies outlined at the beginning of this report, 20 were subjected to special laboratory examinations after withdrawal of thyroid therapy. The results of some of these have been given previously where pertinent to the discussion of special cases. The age range at the time of return in 1956-1957 was from 19 months to 32 years. From these studies the following facts can be ascertained. Of the 31 patients, 8 had some thyroid tissue (approximately one-quarter). Four of the eight had goiters, but one of these did not take up an appreciable amount of I^{131}. All of these eight cretins had protein-bound iodine values of less than 3.0μg. %. Nineteen of the patients and their parents had paper chromatography studies of serum butanol-extractable iodine compounds. All of the cretins, except the two siblings, children of the athyroid mother, had minimal or absent quantities of thyroxin and somewhat larger quantities of iodide. The two exceptions did have easily measured but below-normal quantities of thyroxin and triiodothyronine. It is therefore possible to state that, in our series of 19 patients so studied, 75% fall into the group of athyroid cretins. With the exception of the relatively athyroid mother, none of the parents had abnormal findings for I^{131} uptake, protein-bound iodine, basal metabolic rate, or paper chromatography.

Comment

"Diagnosis of cretinism at the earliest possible date is of the utmost importance, because upon early diagnosis hangs the success of treatment" was stated by J. H. Means in 1937.[16] More recent studies as well as our own experience confirm this statement. It is indeed unfortunate that in many instances the diagnosis of cretinism is not made until well after the optimum time to begin therapy. All of the patients in the present report were referred to us for the establishment of diagnosis and proper therapy. Forty-five per cent were not recognized by the referring physician as having congenital hypothyroidism until after the end of the first year of life. As previously stated, the average age at the time of diagnosis was 12 months. What is the reason for the delay, and how can it be remedied?

Cretinism is not a rare disease. In a 20-year period prior to March, 1956, Wilkins [6] reported that 133 patients with congenital hypothyroidism were seen in the pediatric endocrine clinic of the Harriet Lane Home of the Johns Hopkins Hospital. In the past 10 years in the University Hospital, University of Michigan, we have seen a total of 32 patients in whom this diagnosis was made. Next to diabetes mellitus, hypothyroidism is the commonest endocrine dysfunction in childhood, and a very large majority of the cases are of the congenital type.

Until fairly recently there has been a general feeling of pessimism as to the prognosis in this condition. Talbot et al.[17] state that "only about 25 per cent of the patients who develop signs of thyroid deficiency before the age of two ever attain an intelligence quotient above 80." Gesell and Amatruda [18] also comment that the results of thyroid therapy are seldom satisfactory so far as mental development is concerned, and they give an opinion that the age at which treatment is started is not of great importance, though it "is highly desirable" to make a timely diagnosis. Other authors have similarly cautioned that mental prognosis is usually poor.[19,32] It is probably this misconception that has led to the idea that early diagnosis and treatment are relatively of minor importance. The reports of Smith et al.,[20] Hurxthal,[21] Kerley,[22] Brown et al.,[23] Lewis,[24] and ourselves,[39] plus the animal experiments of Pickering,[25] all tend to disprove the bleak outlook assumed by many physicians and again lay stress upon early diagnosis as well as adequate treatment. An analysis of the data presented by our 49 cretins may be useful in pointing to a prompt diagnosis.

From our series of patients it would appear that a positive history of thyroid disease in the family is significant. We had no control group, but Childs and Gardner [26] made a similar study of 88 cretins and found that the incidence of thyroid disorder in relatives was higher than in a similar control group. Most significant in our study was the occurrence of four families in which another sibling was affected with congenital hypothyroidism, an incidence of about 10% in the 42 families. Childs and Gardner had two families with cretinous siblings. In a study of 36 institutionalized cretins [27] we found three families with two or more siblings similarly affected. These findings suggest a hereditary tendency. We have been unable to find any other genetic studies concerning sporadic cretinism, except in one or two families.[40,41]

In contrast to the report of Childs and Gardner, who found that their cretinous infants were commonly the result of a third or later pregnancy, the majority of our patients were the result of a first pregnancy. Although the birth weights of our cretins averaged 8 lb., slightly more than most mean figures given for normal birth weights in this country, the variation was so great and the weight was so frequently within normal limits that this finding has extremely limited value. Such factors as age of mother, number of siblings, and frequency of congenital anomalies in the family were of no apparent diagnostic value.

In our survey we believe that one of the most important facts revealed was that 54% of the patients had at least three prominent symptoms by the end of the first month of life and 75%, by the end of the third month. The most prevalent of these are given in Table 3.

Such features of cretinism as myxedema, with coarsened features, broad nose, short extremities, protuberant abdomen, myxedematous pads over the shoulders and spatulous hands, appear much later, and to delay diagnosis until these findings are present

TABLE 3.—*Early Clinical Findings* *

	Present in 1st Mo., %	Present in 3d Mo., %
Feeding difficulties	62	70
Respiratory difficulties	58	68
Failure to gain weight	45	72
Lethargy	37	64
Constipation	34	70
"Classical" myxedema	13	40

* Early clinical findings in 39 cretins in which the time of onset of the clinical findings could be accurately judged. The so-called "classical" syndrome of cretinoid features with myxedema is included to show that it is seldom apparent during the first few months of life and that its appearance indicates an unnecessary delay in diagnosis and treatment.

may do irreparable harm to the development of the central nervous system. The same statement may be made with regard to behavior; that is, it is detrimental to the patient to wait for marked retardation of motor development to become evident before entertaining the diagnosis of congenital hypothyroidism.

Many of the early findings in the cretin are relatively nonspecific, such as feeding difficulties, failure to gain weight, constipation, and lethargy. However, when the whole galaxy of these appears, as our analysis indicates to be the rule rather than the exception, then the diagnosis should be established with little difficulty. It is our impression, from interviewing parents, that one of the major reasons for delay was failure of the physician to recognize the clinical entity until after the "full-blown" picture was present.

Some very early physical findings, while not specific for cretinism, should put the physician on the alert for further developments. Umbilical hernia, although found in other abnormal conditions and in normal newborn infants, was much commoner in these infants than in the group of "well babies." Prolonged icterus appearing one to four days postnatally and lasting for over two weeks was first associated with cretinism by Akerren [30] and later by Christensen.[31] The cause is not known but was postulated by these authors as simply prolongation of icterus neonatorum due to liver and possibly kidney immaturity augmented by hypothyroidism. Although this finding was not common in our series of

patients, the incidence of 12% was sufficiently high to make cognizance of this association important.

We would emphasize the frequency with which respiratory difficulties in varying degrees were present in our patients. Usually they were recurrent or persistent, and they were associated with some cyanosis in 15 of the infants. In addition, these patients were subject to an inordinately large number of respiratory tract infections. A review of the literature fails to bring out recognition of this important symptom complex.

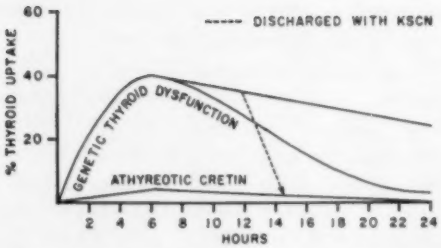
Hurxthal[21] states that "the first signs by which cretinism can be recognized in infancy are the failure to cry normally, to nurse well and a tendency to sleep most of the time." He adds that umbilical hernia is often present. Others have indicated constipation as an early finding.[29] In this group of findings one should certainly include noisy or difficult respiration. Panos,[32] in a study of 15 cretins, emphasizes in addition the failure to gain weight and dry skin as signs frequently present in the first month. If these signs and symptoms are recognized and the possibility of congenital hypothyroidism is considered by the observer, a considerable number of infants can be spared the ill effects of delay in therapy.

The incidence of congenital goitrous cretinism in our series was 8.0%. Gordon[33] reported an incidence of approximately 5.0% in 1922, and Wilkins[6] reported 7.5% in his total series of congenitally hypothyroid children. From these statistics it becomes apparent that defective synthesis of thyroglobulin, which is probably responsible for each of these cases, although not proven in Gordon's series, is a relatively common cause of thyroid deficiency in this country. The presence of a goiter at birth should make one aware of this possibility. However, in a fairly large number the goiter does not become apparent upon physical examination until months or years after the other signs of hypothyroidism are present.

The finding of sparse, brittle, or coarse hair was rare, even in the cretins who had been untreated for many months. It is therefore unfortunate that these clinical findings are given such diagnostic importance in most of the standard texts and reviews.[6,19,29]

Once the diagnosis of cretinism is entertained it can be confirmed by several laboratory techniques. We have found the most valuable to be the determination of serum protein-bound iodine; I^{131} uptake by the thyroid or, more specifically, the absence of uptake, and roentgenograms to measure bone maturation. The first two are more specific, but the last has considerable value, especially as a screening test for determining the advisability of further studies. It also has an advantage over the other two in being more universally available.

In all of the patients in which a determination of protein-bound iodine was obtained the value was below normal at the time of the initial examination, and it was below normal in 18 of the patients who returned to the hospital for the special study and had stopped taking all medication for at least six weeks prior to the test. A small number of cretins have been reported to have a normal protein-bound iodine level if a synthesis defect is present.[7,29] These patients do trap some iodine in the gland and produce iodinated protein compounds such as diiodothyronine and monoiodothyronine, which have ineffectual calorigenic properties. The normal hormone is not formed at all or is formed in very small quantities. Paper chromatography methods to separate these various iodinated proteins are available and are necessary to establish an absolute etiologic diagnosis.[7,34] The patients so far reported in this category have all been goitrous. We were unable to demonstrate this defect in any of our patients, with the exception of the two cretins born to the relatively athy-



Radioiodine uptake in cretinism. Types of radioactive iodine uptake curves of the thyroid or neck area that may be encountered in various forms of congenital hypothyroidism. It will be noted that an initial normal uptake may be present in some types of genetic (enzymatic) thyroid dysfunction. The use of potassium thiocyanate to "wash out" free iodine from the gland is indicated by the broken line.

roid mother. These patients are probably genetically disposed to this chemical abnormality.

Radioactive iodine uptake by the thyroid was markedly depressed in all but four of our patients. Three of these had palpable and visible goiters, and one did not. All of these patients had relatively normal uptakes at 1 to 4 hours but well below normal uptakes at 24 hours. It has been postulated that such patients have thyroids capable of picking up the iodine but that an enzymatic defect in the thyroid prevents the synthesis of the thyroid hormone and the iodine is rather rapidly released either as iodine or as a precursor of the complete hormone.[7] Another type, which was not encountered in this study, is the goitrous hypothyroid patient with a normal uptake of free iodine and enough retention to produce a nearly normal curve but failure to form thyroxin. This free iodine can rapidly be discharged from the gland with potassium thiocyanate (Figure). These genetic thyroid dysfunctions must be differentiated from one another by more extensive studies, such as the use of chromatography to identify the presence or absence of hormone precursors or other abnormal iodinated amino acids.[34] It should be borne in mind that the mutational and the carcinogenic effects of radiation are poorly understood, and the routine use of I^{131} is to be deplored. On the other hand, uptake studies should not be withheld when indicated as an important tool to make an early diagnosis of thyroid deficiency. With the use of sensitive scintillation counting the radiation exposure can be greatly reduced. Doses as small as 1μc. can be used in newborn infants with the approval of the Atomic Energy Commission. We believe that in most instances the determination of the protein-bound iodine or butanol-extractable iodine is sufficient.

In all of the patients adequately examined by roentgenographic methods for bone maturation there was retardation. Delay in appearance of epiphyseal centers is not specific for hypothyroidism, and the diagnosis cannot be confirmed by this method alone, but, since it is always present in this condition, the absence of delay is extremely strong evidence against the diagnosis. Obtaining the appropriate film, knee and foot in early infancy and the carpal areas after the age of 6 or 7 months, therefore, becomes a valuable screening technique. If epiphyseal dysgenesis is seen, according to Wilkins,[15] the diagnosis is then established. He states that this finding is present only in congenital hypothyroidism.

Other laboratory procedures may be used but seldom are as specific as the three outlined. Alkaline phosphatase is reduced below normal in about 90% of cretinous infants, according to Talbot,[35] and our findings confirm this. Other conditions which may lower the serum alkaline phosphatase, such as scurvy and extreme malnutrition, can usually be eliminated upon clinical grounds. When protein-bound iodine determinations cannot be obtained or cause unnecessary delay, the alkaline phosphatase level may be considered as a confirmatory test.

It has been repeatedly pointed out that the serum cholesterol is not elevated in hypothyroidism in the first 6 to 9 months of life.[17,36] It is unfortunate that this fact is not better known, as we encountered several instances wherein therapy was delayed

in early life because of a "normal" cholesterol level.

The use of thyroid in a therapeutic trial is fraught with many difficulties. By implication, it means that the diagnosis has not been definitely established. This usually means withdrawal of therapy at some later date so that laboratory tests can be accomplished to prove the diagnosis beyond doubt. It produces a degree of anxiety in parents, because they are not sure that medication is needed and yet they have misgivings later if they are told to withhold therapy. This practice has also led to the employment of thyroid in a host of children with one or more features bearing some resemblance to cretinism. One could compile a very long list of conditions in which thyroid has been used. In such circumstances false hopes have been given to parents, for example in Mongolism. The combination of a carefully obtained history, adequate physical examination, and the use of a few laboratory procedures is sufficient to make a diagnosis of congenital hypothyroidism.

Summary

The findings in a group of 49 cretins studied at the University Hospital have been presented in an attempt to find as many criteria as possible that will lead to the earliest diagnosis. An analysis of the data leads to the following conclusions.

Important signs of cretinism become apparent by the third month in a very high per cent of these infants. The most commonly observed findings, in order of frequency, are lethargy; constipation; feeding problems, which included slow feeding, choking, failure to gain weight, and lack of interest; respiratory difficulties; umbilical hernia, and skin changes. Three or more of these were present in over 50% of the patients by the end of the first month and in 75% by the end of the third month. The classical picture of the myxedematous cretin does not emerge until later.

The cause for delay in diagnosis is difficult to ascertain, but it is our impression that two of the most important factors can be attributed to the physician. He may wait for the "full-blown" development of cretinism to be sure of his diagnosis. He may have had the misconception that the time of diagnosis makes relatively little difference in the ultimate prognosis. There is enough evidence available at present to prove that this is a very grave error.

The incidence of thyroid disease in the families of cretins is greater than in the general population.

The occurrence of more than one sibling with congenital hypothyroidism is not uncommon. It occurred in 9% of our families.

The course of pregnancy and labor resulting in a congenitally hypothyroid infant is not remarkable in most instances.

There is no characteristic birth order in congenital hypothyroidism.

Seventy-five per cent of our congenitally hypothyroid children were of the athyroid type. Eight per cent were born with or developed goiters in infancy or early childhood. An error in the synthesis of the hormone was proven in all but one of the goitrous patients and was probably present in the one exception, but tests could not be completed.

The estimation of the serum protein-bound iodine or butanol-extractable iodine is the most valuable laboratory test to establish diagnosis because of its reliability and the fact that exposure to radioactivity is avoided. This last factor is the only serious limitation to the use of I^{131} uptake by the thyroid, which is an equally reliable diagnostic procedure. In goitrous patients, and possibly in a small number without goiter formation caused by errors in synthesis of the thyroid hormone, laboratory determinations in addition to those of protein-bound iodine and I^{131} uptake may be necessary to establish a definite diagnosis. The more exact identification of iodinated compounds in the blood is then required.

The evaluation of bone maturation is a valuable screening device. Every patient

adequately examined by x-ray for "bone age" had easily measured retardation. Without the finding of delay in appearance of ossification centers one can strongly doubt the diagnosis of hypothyroidism.

We believe that the therapeutic trial of thyroid in infants and children as a means of diagnosis is no longer a desirable procedure.

Diagnosis of cretinism usually can be made by 3 months and certainly before 6 months of age, with the aid of careful history, adequate physical examination, and a very few laboratory procedures.

University Hospital.

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Butanol-Extractable Iodine Values in the Offspring of Diabetic Women

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Infants born of women with diabetes mellitus often present serious problems and have an increased morbidity and mortality. Studies of these infants and of the mothers during their pregnancies have failed to reveal the pathogenesis of the phenomena that occur among the infants. It has been suggested that such changes are related to a disturbance of maternal sex harmones, but the exact alterations or specific manner in which they affect the infant have not been determined. The present report is concerned with studies of butanol-extractable iodine (BEI) values in the serum of infants born of diabetic women who did not receive any sex-hormone therapy during pregnancy. The data, although limited and of a preliminary nature, are offered at this time to enable others who have access to more clinical material to follow up these studies.

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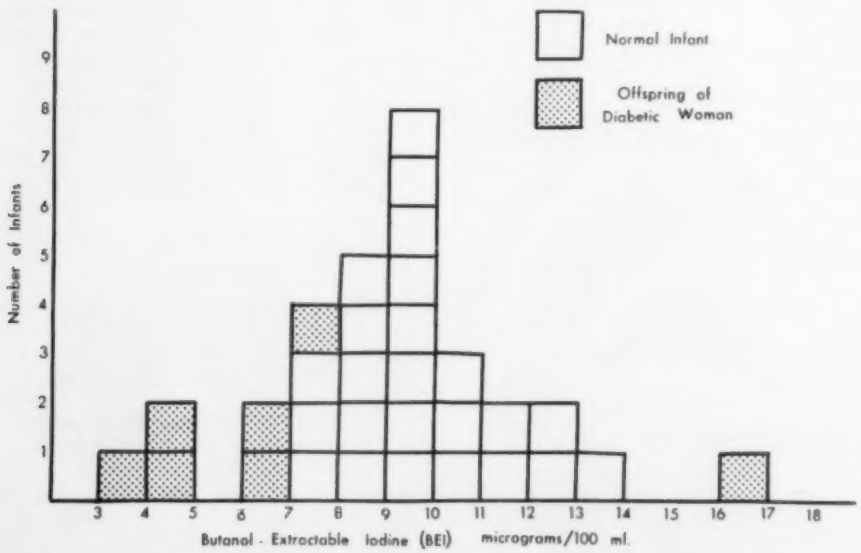
Method

Assays for serum BEI were performed on blood obtained immediately after birth from the umbilical cord and from the femoral vein when the infants were 5 days old. Studies were carried out at these particular periods because they represented the only two times during the first month of life for which normal standards have been determined in our laboratory. The technique of assaying the serum for BEI has been described by Man and co-workers.[1]



Butanol-extractable iodine (BEI) levels in the serum of 5-day-old normal infants and in the offspring of diabetic women.

Butanol-Extractable Iodine at Five Days of Age *

BEI, μg/100 Ml.	Infants of Normal Mothers	Infants of Diabetic Mothers	Total
Below 7.2	0	5	5
Above 7.2	24	2	26
Total	24	7	31

* χ^2-Test gives a value of 15.5 when calculated with Yates correction for the 2×2 contingency table, with use of the results of the assays of BEI of all seven of the infants born of diabetic mothers. This corresponds to a probability of far less than 1% for the random occurrence of such a distribution.

Results

The results of determination of the BEI levels at 5 days of age are plotted in the Figure. The same results are arranged in a form suitable for statistical evaluation in the Table. Even though the number of infants in the abnormal group is few, there is a highly significant difference in the BEI levels from those of normal infants.* Five of the seven infants born of diabetic mothers had BEI levels lower than those found in any of the normal newborn infants tested, while one child had a level at 5 days of age which was 2.8μg/100 ml. higher than that found in any of the normal newborn infants. Assays for BEI were also performed on the cord blood of three of these seven infants, and the results were normal in all.†

The determination of butanol-extractable iodine measures the iodine of thyroxin-like substances of serum without that of diiodothyronine or of inorganic iodine. Therefore, it is felt to be a more accurate measure of thyroid activity than the measurement of iodine precipitated with serum proteins (PBI).[1] In our laboratory assays of BEI in blood obtained from the umbilical cord of normal infants have been found to contain between 3.7μg. and 10.3μg/100 ml.[2,3] The levels at five days of age range between 7.2μg. and 13.2μg/100 ml.[4]

Danowski et al.[5] also found that the levels of iodine (as PBI) in the blood of normal children 1 to 7 days old were significantly higher than those which prevail immediately following birth.

Comment

There is as yet no unanimity of opinion as to the etiology of the basic disturbance in the infant born of a diabetic mother. Many investigators have speculated that the disorder in these infants represents some endocrine imbalance in the mother, but the basis of this belief has often been tenuous and subjective. White and co-workers[6-9] have postulated that the alterations present in the infants may be due to some endocrine imbalance, and they believe that administration of female hormones during pregnancy may restore a normal endocrine balance and improve fetal survival. Others[10,11] have suggested that the abnormalities in the offspring of diabetic mothers are due to maternal pituitary imbalance, perhaps as a result of overproduction of growth hormone. However, most experimental studies have shown that the injection of growth hormone into various pregnant animals has not yielded heavier than normal offspring[10-12] and such changes do not occur among the offspring of acromegalic women.

Farquhar[13] and Jackson[14] believe that the clinical picture in the infants born of diabetic women is due to still another disturbance of endocrine function namely, an alteration involving the newborn infant's adrenal cortex. Farquhar's studies provide some evidence that adrenocortical activity may be greater in the fetus of the diabetic

* The single high value (16.1μg/100 ml.) in the offspring of diabetic women differs from the mean of the remaining six by six times the value of the standard deviation computed only from the six lower levels. The standard deviation of these six was 1.78. The probability of a random deviation of this magnitude is less than 1% according to a *t*-distribution with five degrees of freedom. On this basis, the value 16.1 can be omitted from the calculation of the significance of the results in the offspring of the diabetic mothers. When the mean of the remaining 6 assays is compared with that of the 24 control assays the difference is found to be significant to better than 0.5% by *t*-test with five or more degrees of freedom.

† Assays for BEI in the serum of infants born of mothers with other compensated endocrine disturbances were all normal.

than in that of the nondiabetic woman, and he suggests that there is clinical evidence that hyperadrenocorticism plays some part in producing the morphological features of the fetus of the diabetic woman.

No ready explanation is available to account for the abnormally low levels of butanol-extractable iodine found at 5 days of age in five of seven infants born of diabetic women whom we studied or for the very high level in one of the seven infants. It may be that the pregnant woman with diabetes mellitus produces an excessive quantity of various hormones. This overproduction may continue throughout pregnancy or cease gradually or abruptly at any time during gestation. During the period that these hormones are being produced in excess, they may act by crossing the placenta and stimulating the appropriate fetal organ to produce its own hormone(s); they may act directly on the fetus itself and be associated with an inhibition of the appropriate fetal organ to produce its own hormone(s), or they may act directly on the fetus itself and be associated with an inhibition of the appropriate fetal endocrine gland. Although the literature contains conflicting and inconclusive reports regarding the transfer of thyroid hormones across the placenta,[2,15-17] a recent report [18] indicates that the human placenta is capable of transmitting significant amounts of thyroid hormones, with the transport of triiodothyronine appearing to be more rapid than that of thyroxin.

Other explanations for the low levels of BEI are that they result from increased adrenocortical activity,[13] with a resultant inhibition of the thyroid gland,[19] or that they are secondary to changes in the liver, with a temporary increased elimination and inactivation of thyroid hormones.[20,21]

Summary

Abnormally low butanol-extractable iodine (BEI) levels were found at 5 days of age in the serum of five of seven infants born of women with diabetes mellitus.

Possible mechanisms producing these findings are discussed.

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Dr. E. Man, of the Department of Medicine, Yale University School of Medicine, carried out the assays of BEI and gave many suggestions; Drs. Morris Krosnick, Paul Goldstein, and Sidney Hurwitz, of the Department of Pediatrics, Yale University School of Medicine, gave permission to study some of the patients, and Dr. Leonard Lerman, of the Department of Biophysics, University of Colorado School of Medicine, assisted with the statistical analysis.

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Studies on Copper Metabolism

XXIV. Hypocupremia in Infancy

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Hypocupremia has been observed occasionally in patients with severe microcytic hypochromic anemia due to iron deficiency,[1-5] but as a rule the serum copper is increased in iron deficiency.[1,6] It was, therefore, of interest when Sturgeon and Brubaker[7]; Ulstrom, Smith and Heimlich,[8] and Lahey[9] described a syndrome characterized by hypocupremia, hypoferremia, hypoproteinemia, edema, and hypochromic microcytic anemia in a total of 19 infants and children.

Sturgeon and Brubaker[7] treated one of their patients with copper and noted a prompt increase in serum copper but no increase in hemoglobin, reticulocytes, or serum proteins. Lahey[9] made a similar observation in two of his patients. In addition, Lahey observed that the administration of iron alone was followed by a prompt reticulocystosis, alleviation of anemia, and an increase in serum proteins but no increase in serum copper. The diets of the patients studied by Sturgeon and Brubaker and by Lahey had consisted almost exclusively of homogenized milk. Consequently, it was suggested that a nutritional inadequacy of both iron and copper might be of primary importance in the pathogenesis of the syndrome. Because correction of the hypoproteinemia followed the administration of iron alone, Lahey postulated that the hypoproteinemia might be secondary to the iron deficiency. In support of this thesis was the finding of hypoalbuminemia in about about one-third of 25 infants with severe iron-deficiency anemia and normal serum copper levels.

The patients studied by Ulstrom, Smith, and Heimlich,[8] in contrast to those studied by the other workers, had taken a normal diet during the development of the anemia and hypoproteinemia. Furthermore, recovery took place without recognizable changes in the diet. These workers therefore suggested that the disturbance was not primarily of dietary origin but represented a new syndrome which they called "transient dysproteinemia in infants." They suggested that the hypocupremia might be a reflection of the low globulin content of the plasma.

The purpose of this paper is to describe three infants with anemia, hypoferremia, hypocupremia, and hypoproteinemia and to present the results of studies concerning the pathogenesis of the hypocupremia. Current knowledge of the multiple causes of hypocupremia in infants and children will be summarized. It is apparent from our own observations that at least two different types of disorder are involved in the production of hypocupremia in hypoproteinemic infants. This possibility was suggested earlier by Lahey[9] as well as by Brubaker in the discussion of Lahey's paper.[10]

Methods

The methods for the determination of serum and erythrocyte copper,[11] ceruloplasmin,[12] serum iron,[13] total iron-binding capacity,[14] and urine and stool copper[15] have been described in previous publica-

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From the Department of Medicine, University of Utah College of Medicine. John S. McEachern Fellow, Canadian Cancer Society (Dr. Zipursky) and Medical Research Fellow, Canadian National Research Council (Dr. Dempsey).

tions. Total serum protein estimations were performed by a modification[10] of the method described by Weichselbaum.[37] Filter-paper electrophoresis of the serum proteins was carried out by the use of Spinco Model R apparatus. Proline tolerance tests were performed by the method of Gould and Schwachman.[38]

The homogenized milk used in these studies contained 0.024 mg. of copper per liter of milk. The iron-dextran preparation used contained 5μg. of copper per milliliter.

Report of Cases

CASE 1.—A boy was admitted to the Salt Lake County General Hospital for the first time at the age of 8½ months. He had been well until 5 months of age, when he developed an upper respiratory infection and was found by his private physician to be anemic. He was treated with "liver shots" and an oral iron preparation; the latter was continued for two and one-half months. During the month prior to admission he had become progressively more pale and listless. Two days prior to admission puffiness of his eyes was first noticed. The pallor, edema, and listlessness persisted, and he was admitted to the hospital on March 9, 1957.

The patient weighed 8 lb. 7 oz. at birth and was the product of a 37-week gestation. The mother was said to have been anemic during her pregnancy and to have improved with iron therapy. The child had been breast-fed until 5 months of age and was then given a homogenized milk formula.

TABLE 1 (Case 1).—*Summary of the Hematologic and Biochemical Observations at the End of Each Period*

Determination	Period I No Therapy	II Iron	III Copper	IV Iron
Hemoglobin, gm./100 ml.	3.7	10.3	8.1	10.1
Mean corpuscular volume, cu. μ.	54	84	67	79
Mean corpuscular hemoglobin, conc., %	22	28	28	28
Reticulocyte, maximum, %	8.7	32.9	4.9	11.5
Serum iron, μg./100 ml.	14	46	27	72
Serum copper, μg./100 ml.	56	48	205	137
Ceruloplasmin, mg./100 ml.	21	23	35	31
Erythrocyte copper, μg./100 ml.		104	143	112
Total protein, gm./100 ml.	5.6	6.5	6.8	6.8
Albumin, gm./100 ml.	2.1	4.0	4.1	3.4
α_1-globulin, gm./100 ml.	0.4	0.3	0.5	0.5
α_2-globulin, gm./100 ml.	0.9	0.7	0.8	1.0
β-globulin, gm./100 ml.	0.9	0.8	0.9	1.1
γ-globulin, gm./100 ml.	1.3	0.7	0.6	0.9

He continued to take 2 qt. of milk daily, with little solid food. There is one older sibling who is well. The remainder of the history is noncontributory.

The patient was a pale irritable infant, 28 in. in height and weighing 16½ lb. There was slight pretibial and moderate periorbital edema. The liver was palpated 2.5 cm. below the right costal margin. The spleen was felt 1 cm. below the left costal margin. No other abnormalities were found on physical examination.

The pertinent laboratory data on admission are presented in Table 1 (Period I). The total iron-binding capacity of the serum was 350μg/100 ml.

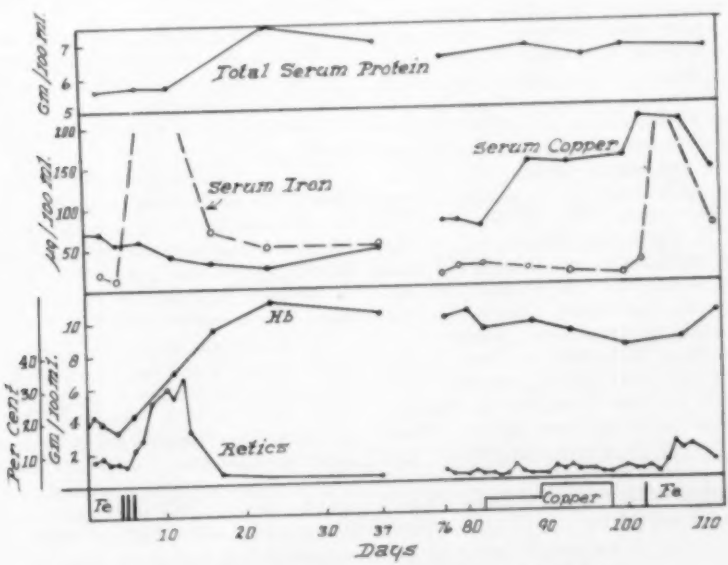

Fig. 1 (Case 1).—Response to the administration of iron and copper.

The leukocyte count was 13,900 per cubic millimeter. The differential leukocyte count was as follows: neutrophils, 13%; lymphocytes, 82%; monocytes, 5%. The bone marrow differential count was not remarkable except for a reduction in the myeloid-erythroid ratio from the normal of 3:1 to 1.2:1. Polychromatophilic normoblasts predominated. Direct and indirect Coombs' tests were negative. Fecal urobilinogen was 7.7 mg. per day. Stool examinations were repeatedly negative for occult blood. Urinalyses were repeatedly normal. X-ray studies of the chest, long bones, and large bowel revealed no abnormalities. Other laboratory determinations included blood urea nitrogen, van den Bergh test, serum calcium, cephalin-cholesterol flocculation, and sulfobromophthalein (Bromsulphalein) excretion, all of which were within normal limits.

Throughout the entire hospital admission the patient was given a diet which consisted of only homogenized milk and a supplement of vitamins A and D and ascorbic acid. Period I consisted of a four-day control period. During this time the volume of milk consumed was measured and all stools and urine were collected. The copper concentration of the milk, urine, and stools was measured. During this period the daily copper intake averaged 26μg. The average daily excretion of copper in the urine was 11μg., and in the stools, 80μg. Thus, the daily excretion of copper exceeded the daily intake by 65μg.

On each of the next three days the patient was given 100 mg. of iron in the form of iron-dextran, intramuscularly. Reticulocytes were counted daily, and total serum proteins, hemoglobin, serum iron, and serum copper were measured at appropriate intervals for a period of 33 days. The results are presented in Figure 1. The data at the end of this period (Period II) are summarized in Table 1.

After the administration of iron the reticulocytes increased and reached a maximum of 33% eight days after the first injection of iron. The reticulocytosis was accompanied by an increase in the hemoglobin concentration from 3.7 gm/100 ml. to 10.3 gm. The microcytosis disappeared, and the cells became less hypochromic, although the mean corpuscular hemoglobin concentration did not return to normal. Immediately after the administration of iron, the serum iron increased to a maximum value of 5872μg/100 ml. This was followed by a rapid and then a somewhat more gradual decline to a level of 46μg/100 ml. Throughout this period the serum copper did not increase and varied between 26μg. and 59μg/100 ml. The total serum proteins increased to within normal limits as a result of an increase in serum albumin from 2.1 to 4.0 gm/100 ml.

At the insistence of the parents, the child was removed from the hospital for a period of 40 days. During this time he received a diet which consisted only of whole milk. He remained in good health, and at the time of readmission the physical examination was not remarkable except for a liver palpable 2 cm. below the right costal margin, a spleen which was palpable 1 cm. below the left costal margin, and mild injection of the pharynx and both tympanic membranes. The hemoglobin was 10 gm/100 ml.; serum copper, 81μg/100 ml.; erythrocyte copper, 75μg/100 ml. of packed cells; total serum protein, 6.5 gm/100 ml.; serum albumin, 4.9 gm/100 ml., and serum iron, 17μg/100 ml.

The infant was again fed only homogenized milk with a supplement of vitamins A and D and ascorbic acid. Starting on the sixth day after readmission, he was given 600μg. of copper per day by mouth in the form of copper acetate. Eight days later the copper was increased to 2000μg. per day. This amount of copper was given for 10 days. The results are presented in Figure 1. The data at the end of this period (Period III) are summarized in Table 1.

The administration of copper was not followed by reticulocytosis, an increase in hemoglobin, or alleviation of the hypoferremia. However, the serum copper increased from 81μg/100 ml. to 205μg. and the ceruloplasmin level increased from 23 to 35 mg/100 ml.

During the next period (Period IV) the patient was given a single intramuscular injection of 100 mg. of iron in the form of iron-dextran. This was followed by an increase in reticulocytes to 11.5% and a rise in serum iron to 964μg/100 ml. (Fig. 1).

The patient was discharged from the hospital on the 10th day after the administration of iron. The final values (Period IV) are given in Table 1. Unfortunately, the family moved from the state at that time and the patient has not been seen again.

CASE 2.—A girl was admitted to the Salt Lake County General Hospital for the first time at the age of 6 months. The patient had been well until one week before admission, when she became pale, listless, irritable, and anoretic. Three days prior to admission she began to vomit and had occasional loose bowel movements.

She was the only child of an 18-year-old mother, whose pregnancy had been normal and full term. The delivery was uneventful, and the child weighed 7 lb. 10 oz. at birth. She was breast-fed until 2 months of age, when she was given an evaporated milk formula. Solid foods were begun at 2½ months of age and were taken well. By 6 months of age she was taking three cans of solids daily, including egg yolk, meat, and fruits. A vitamin supplement had been given since birth. The remainder of the history was noncontributory.

TABLE 2 (Case 2).—*Summary of the Hematologic and Biochemical Observations at the End of Each Period*

Determination	Period I No Therapy	II Transfusion	III Iron	IV Copper
Hemoglobin, gm./100 ml.	4.1	9.0	12.5	10.2
Mean corpuscular volume, cu. μ.	56	72	85	70
Mean corpuscular hemoglobin conc., %	25	29	30	29
Reticulocyte, maximum %	8.6	4.5	11.9	5.8
Serum iron, μg./100 ml.	27	23	61	21
Serum copper, μg./100 ml.	57	66	87	167
Ceruloplasmin, mg./100 ml.	19		21	33
Erythrocyte copper, μg./100 ml.	66	91	103	164
Total protein, gm./100 ml.	5.5	6.7	7.9	7.0
Albumin, gm./100 ml.	2.3	3.4	3.8	3.8
α_1-globulin, gm./100 ml.	0.4	0.4	0.4	0.3
α_2-globulin, gm./100 ml.	0.8	0.8	1.4	0.7
β-globulin, gm./100 ml.	1.1	1.1	1.0	1.2
γ-globulin, gm./100 ml.	0.9	1.0	1.3	1.1

Physical examination revealed pallor and minimal edema of the pretibial and periorbital tissues. The liver edge was palpable 2 cm. below the right costal margin. The spleen tip was just palpable at the costal margin. The remainder of the examination, including sigmoidoscopy, was negative.

The pertinent laboratory data on admission are presented in Table 2 (Period I). The leukocyte count on admission was 37,700 per cubic millimeter, but all subsequent counts were normal. The differential leukocyte count was as follows: neutrophils, 13%; basophils, 1%; lymphocytes, 86%. The bone marrow was not remarkable except for a myeloid-erythroid ratio of 1.6:1. Polychromatophilic normoblasts predominated. Serum calcium, phosphorus, bilirubin, alkaline phosphatase, blood urea nitrogen, and prothrombin time were within normal limits. Occult blood was found repeatedly in the stools on the first five hospital days but not thereafter. X-ray studies of the upper and lower gastrointestinal tract revealed no abnormalities.

The patient was fed homogenized milk and a supplement of vitamins A and D and ascorbic acid. This diet was maintained throughout the entire hospitalization. Because of the severe anemia, she was given a transfusion of 100 ml. of washed red blood cells on the second hospital day. The transfusion was followed by an increase in the hemoglobin level to 9 gm/100 ml. and by an increase in the total serum protein concentration. The values six days later are summarized in Table 2 (Period II).

On the eighth hospital day she was given 60 mg. of iron in the form of iron-dextran intramuscularly. Two days later a second injection of 100 mg. of iron was given intramuscularly. The hematologic and biochemical studies performed 18 days after the second injection of iron are summarized in Table 2 (Period III).

After the administration of iron the reticulocytes increased and reached a maximum value of 11.9% on the sixth day following the beginning of iron therapy (Fig. 2). The reticulocytosis was followed

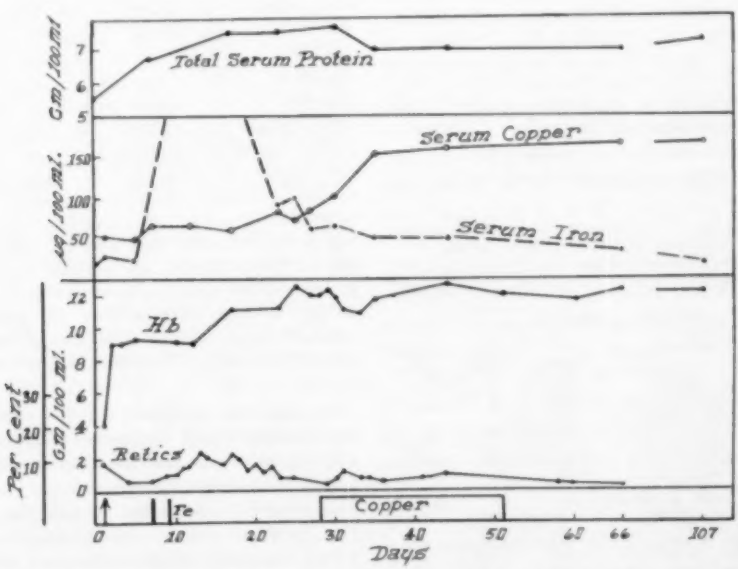

Fig. 2 (Case 2).—Response to the administration of iron and copper. The arrow refers to the transfusion of 100 ml. of packed red cells.

by an increase in the hemoglobin level from 9 to 12 gm/100 ml. The red cells became normal in size, although a slight degree of hypochromia remained. The serum iron level increased to 5700μg/100 ml. and then decreased rapidly to about 60μg/100 ml. The serum copper and ceruloplasmin concentrations increased only slightly, from 66μg. to 87μg/100 ml. and from 19 to 21 mg/100 ml., respectively. The total serum protein concentration increased to 7.9 gm/100 ml. as a consequence of a further increase in the serum albumin concentration (Table 2).

The patient was then given 1000μg. of copper acetate by mouth. This therapy was continued for 15 days. The patient was discharged from the hospital and observed at intervals for a period of 56 days. The values at the end of this period are summarized in Table 2 (Period IV).

The administration of copper was not followed by reticulocytosis (Fig. 2). However, the serum copper and ceruloplasmin concentrations increased from 87μg. to 167μg/100 ml. and from 21 to 33 mg/100 ml., respectively. During the period of copper administration and the subsequent period of follow-up the total serum proteins, serum albumin, and hemoglobin remained within normal limits. There was a progressive decline in the serum iron level from 61μg. to 21μg/100 ml.

CASE 3.—A 4-month-old girl of Spanish-American origin was admitted to the Salt Lake County General Hospital on Nov. 27, 1956. She was born Aug. 1, 1956, following a normal pregnancy and delivery. She appeared well and she developed normally until the age of 2½ months, when diarrhea and irritability first occurred. At 3 months of age swelling of her hands and face were noticed and several episodes occurred which were described by her physician as tetany. At that time she was admitted to another hospital and was found to have a total protein of 2.4 gm/100 ml. and a serum calcium of 6.6 mg/100 ml. One hundred twenty milliliters of plasma was given on Nov. 2, 1956 and again on Nov. 3, 1956, with a resultant rise in total protein to 4.7 gm/100 ml. Three weeks later she was referred to the Salt Lake General Hospital because of the recurrence of hypoproteinemia.

TABLE 3 (Case 3).—*Summary of the Hematologic and Biochemical Observations at the End of Each Period*

Determination	Period I No Therapy	Period II Copper	Period III Copper & Iron
Hemoglobin, gm./100 ml.	10.0	9.0	10.9
Mean corpuscular volume, cu. μ.	95	76	82
Mean corpuscular hemoglobin conc., %	30	28	31
Reticulocyte, maximum %	5.7	9.3	6.0
Serum iron, μg./100 ml.	21	28	68
Serum copper, μg./100 ml.	36	51	117
Ceruloplasmin, mg./100 ml.	11.5		30
Erythrocyte copper, μg./100 ml.	142	143	106
Total protein, gm./100 ml.	2.9	2.9	7.5
Albumin, gm./100 ml.	1.4	0.9	5.4
α_1-globulin, gm./100 ml.	0.3	0.3	0.2
α_2-globulin, gm./100 ml.	0.5	0.9	0.7
β-globulin, gm./100 ml.	0.6	0.6	0.9
γ-globulin, gm./100 ml.	0.2	0.2	0.4

She had been breast-fed until 3 months of age; thereafter she had received an evaporated milk formula. At no time did she receive a vitamin supplement or solid foods. There was no family history of illness. Three older siblings were all well.

Physical examination revealed a small dark irritable infant weighing 12½ lb. and measuring 24½ in. in length. There was 2+ edema of her feet and a moderate degree of periorbital puffiness. The liver was palpated 1 cm. below the costal margin; the spleen was not palpable. The remainder of the examination was normal.

The pertinent laboratory studies on admission (Period I) are summarized in Table 3. The red cells appeared normocytic and normochromic. The total iron-binding capacity of the serum was 138μg/100 ml., and the serum iron, 18μg/100 ml. Thus, the iron-binding protein was 13% saturated. The total leukocyte count was 6400 per cubic millimeter. The differential leukocyte count was as follows: neutrophils, 62%; eosinophils, 2%; basophils, 1%; lymphocytes, 28%, and monocytes, 7%. The bone marrow was not remarkable except for a myeloid-erythroid ratio of 0.9:1 and an absence of plasma cells. Polychromatophilic normoblasts predominated within the erythroid series. The serum calcium ranged from 5.2 to 6.1 mg/100 ml., and the serum phosphorus was 4.7 mg/100 ml. Urine Sulkowitch tests were repeatedly negative, as were routine urinalyses. The blood urea nitrogen was normal. The stools were examined for enteric pathogens, ova, parasites, fat, and tryptic digestion. All of these tests were normal. Sulfobromophthalein excretion, intestinal absorption of iodized oil (Lipiodol), and glucose- and proline-tolerance tests were all within normal limits. X-ray studies of the long bones, upper gastrointestinal tract, and colon revealed no abnormality. A chest x-ray on Nov. 28, 1956, showed minimal apical infiltration bilaterally, suggesting bronchopneumonia. This had cleared completely by Dec. 19, 1956.

On admission the infant was fed a diet of homogenized milk with supplements of cereals, fruits, and vegetables. Because the diarrhea was severe, with 5 to 10 watery bowel movements, solid foods were removed from the diet. Despite this, the diarrhea continued and the patient's condition became worse. Neomycin therapy was started on Dec. 11. On Dec. 16 the patient developed severe tetany, which responded to intravenous and oral calcium.

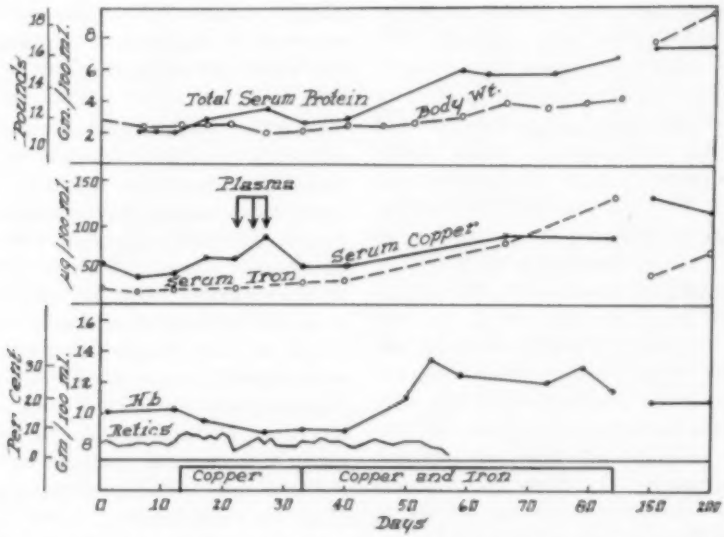

Fig. 3 (Case 3).—Response to the administration of plasma, copper, and copper and iron.

The diarrhea continued in spite of Neomycin therapy, and on Dec. 21 this therapy was discontinued and the infant was treated with tetracycline. The diarrhea still continued. The diet was changed to skimmed milk and rice water. On Dec. 20 oral copper therapy was begun. The child was given 250μg. of copper daily in the form of copper acetate. Beginning Dec. 29, she was given 250μg. of copper intravenously for five consecutive days. Because of continued deterioration in her general condition, she was given 100 ml. of plasma on Dec. 29, Jan. 1, and Jan. 3. This was followed by a slight improvement in her condition. The hematologic and biochemical values after 20 days of copper therapy are summarized in Table 3 (Period II).

The copper therapy was without influence on the total serum protein, copper, or iron concentration (Fig. 3.) There was no reticulocytosis, and the hemoglobin concentration decreased. Following the administration of plasma, there was a slight, transient increase in the concentration of proteins and copper in the serum (Fig. 3).

Oral iron therapy, in addition to copper, was begun on Jan. 9 (Period III). The improvement in the patient's general condition and in the diarrhea which had been noted following the administration of plasma continued. The diet was changed from skim milk to homogenized milk, and solid foods were added. By February the patient had improved greatly, and the diarrhea disappeared completely. She has remained in good health.

The hematologic and biochemical values obtained on June 26, 1957, are summarized in Table 3 (Period III).

Comment

Patients 1 and 2 were similar in all important aspects and differed from Patient 3. Patients 1 and 2 had severe hypochromic microcytic anemia, hypocupremia, and hypoalbuminemia. Serum globulins were not decreased.[19] Following the administration of iron, there was a prompt hematologic response and an appreciable increase in serum albumin. The hypocupremia was not influenced by the administration of iron. The administration of copper was followed by an increase in ceruloplasmin and in the total serum copper to within the normal range for the ages of these patients.[20]

These 2 infants are similar to the 12 described by Lahey[9] and the 5 reported by Sturgeon and Brubaker,[7] except that the infants described by these workers had hypogammaglobulinemia in addition to hypoalbuminemia.

In contrast to Patients 1 and 2, Patient 3 had intractable diarrhea, hypocupremia, severe hypoproteinemia, and hypocalcemia.

The hypoproteinemia was due to a reduction in albumin, β-globulin, and γ-globulin. An anemia of only mild degree was present, and, although hypoferremia was present as in the first two cases, the erythrocyte morphology was within normal limits. Later the erythrocytes became hypochromic and microcytic. This was possibly related to the withdrawal of relatively large amounts of blood for the numerous biochemical studies. The administration of copper to this patient, in contrast to Patients 1 and 2, was not followed by a significant increase in ceruloplasmin or serum copper. Following the administration of iron and copper the diarrhea, hypoproteinemia, hypocupremia, and hypocalcemia improved slowly over a period of several months. It is likely that improvement was spontaneous and not related to therapy with either copper or iron.

The clinical syndrome presented by this patient seems to be similar to that of the four patients described by Ulstrom, Smith, and Heimlich [8] and to the two cases with "chronic enteritis" mentioned by Lahey.[9] The hypocupremia in the two infants studied by Lahey failed to respond to the oral administration of copper. Ulstrom et al. did not give copper to their patients.

Certain deductions can be made concerning the pathogenesis of the hypocupremia in these three infants. About 95% of the copper in normal serum is in combination with ceruloplasmin.[12,21] Therefore, hypocupremia of a significant degree must, of necessity, be due to a decrease in the concentration of ceruloplasmin. That this was the case in the three patients reported here is shown by the direct measurement of ceruloplasmin.

Theoretically, the concentration of ceruloplasmin may be decreased as a result of (1) an inability to synthesize ceruloplasmin or (2) an excessive loss of ceruloplasmin. Ceruloplasmin synthesis could be impaired either as a consequence of a deficiency of copper or as a result of inability to synthesize the protein portion (apoceruloplasmin) of the molecule. Excessive loss of ceruloplasmin could be due either to excessive excretion of copper from the body or an accelerated rate of catabolism within the body.

In patients with hypocupremia due to a deficiency of copper, it would be expected that the hypocupremia would be corrected promptly following the administration of copper. This is true in swine with a dietary deficiency of copper.[22,23] On the other hand, if hypocupremia either is due to inability to synthesize ceruloplasmin as a result of a defect in protein synthesis or is caused by an accelerated rate of breakdown of ceruloplasmin within the body, the administration of copper will not alleviate the hypocupremia. If there were excessive excretion of ceruloplasmin, the administration of copper might or might not be followed by an increase in ceruloplasmin. This would depend upon whether copper depletion or the rate of protein synthesis was the limiting factor.

The hypoceruloplasminemia present in Patients 1 and 2 was promptly alleviated by the administration of copper. Therefore, it is reasonable to assume that the hypocupremia in these two infants was due to a deficiency of copper.

It has been noted in swine fed a diet low in copper that the earliest detectable manifestation of copper depletion is hypocupremia. This is followed by a decrease in red cell copper and later by the development of anemia.[22] Likewise, hypocupremia appears rapidly and prior to the development of anemia in adult rats fed a diet of evaporated milk.[24]

The concentration of copper within the erythrocytes of Patient 1 was within normal limits. This would imply that the deficiency of copper was not severe. Erythrocyte copper was somewhat reduced in Patient 2, suggesting that in this patient the degree of depletion of copper was somewhat greater than in Patient 1. In neither patient is it likely that the depletion of copper was sufficiently great to be of any significance in the pathogenesis of the anemia. This is suggested by the observation that the anemia

responded rapidly and completely to the administration of iron. Swine deficient in both iron and copper respond little or not at all to the administration of iron alone.[22]

It is tempting to conclude that these two infants had a dietary deficiency of copper and protein as well as of iron. However, there are certain considerations which suggest that the explanation may not be as simple as this. Patient 2 had eaten solid foods well since the age of 2½ months. The failure of Patient 1 to ingest solid foods seems inadequate to explain either the hypocupremia or the hypoalbuminemia. Most infants fed only milk do not develop hypocupremia even in the presence of a severe deficiency of iron.[6] Milk is known to be one of the best sources of protein, and infants and swine fed exclusively on milk supplemented with iron do not develop hypoalbuminemia.[22] It is possible that the hypoalbuminemia is related in some way to the deficiency of iron. In support of this hypothesis is our observation and that of Lahey[9] that the albumin concentration increased following iron therapy. In addition, as mentioned earlier, Lahey has observed hypoalbuminemia in about one-third of 25 infants with severe iron-deficiency anemia and normal serum copper values.

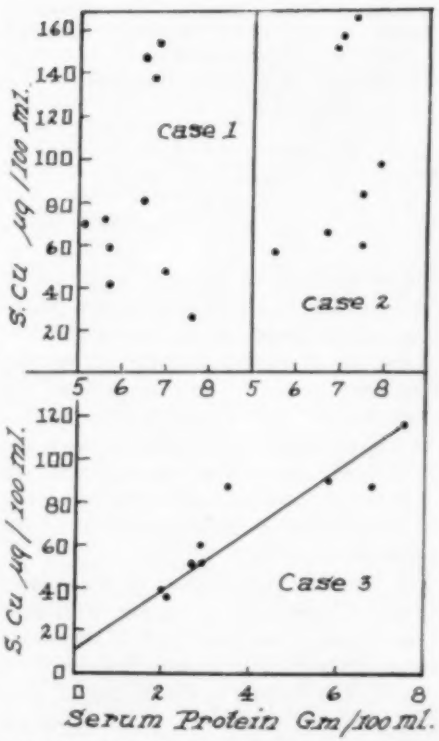

Fig. 4.—Correlation between the total serum copper value and total serum proteins in the three patients.

The hypocupremia in Patient 3 failed to respond to the oral administration of copper. The administration of 1.25 mg. of copper intravenously likewise failed to increase the concentration of copper in the serum. This amount of copper given intravenously to a 10 to 20 kg. pig severely deficient in copper is sufficient to increase the plasma copper level to within the normal range and results in a prompt and complete hematologic remission.[22] Therefore, it would seem likely that in this patient the hypocupremia was not due to depletion of copper and, therefore, must have been due either to a failure to synthesize apoceruloplasmin or to an increased rate of destruction or loss of this protein from the body. That the hypocupremia was related to the hypoproteinemia is suggested by the high degree of correlation (correlation coefficient, +0.91; $P<0.001$) between the concentration of total serum protein and the concentration of serum copper (Fig. 4). A similar correlation has been observed in swine made hypoproteinemic by dietary restriction of protein.[25] Such a correlation has not been observed in swine with a dietary deficiency of copper[22] and was not present in Patients 1 and 2 (Fig. 4).

Studies by Ulstrom, Smith, Nakamura, and Heimlich[26] of plasma protein turnover rates with phenylalanine-3-C^{14} in three of their infants suggest that an increased rate of plasma protein degradation and failure to compensate for it with an increased rate of production were responsible for the hypoproteinemia. Whether the hypocupremia in Patient 3 was due to a defect in the

TABLE 4.—*Classification of Hypocupremia*

I. Inability to synthesize ceruloplasmin
A. Due to lack of copper
B. Due to inability to synthesize the apoprotein
1. Newborn infants
2. Wilson's disease
3. Kwashiorkor
4. Sprue
5. Celiac disease
6. Idiopathic hypoproteinemia
II. Excessive loss or destruction of ceruloplasmin
A. Excretion from the body (nephrotic syndrome)
B. Accelerated rate of catabolism

rate of synthesis of the protein portion of ceruloplasmin, to an increased rate of breakdown of the protein, or to an excessive loss of the copper protein into the gastrointestinal tract cannot be determined from the available data. However, it is apparent that the hypocupremia was associated with the generalized hypoproteinemia and was not secondary to a dietary deficiency of copper or to a failure to absorb copper from the gastrointestinal tract.

A tentative classification of the known causes of hypocupremia is given in Table 4. Conceivably, a lack of copper (I, A) could result from (1) a dietary deficiency of copper, (2) failure to absorb copper from the gastrointestinal tract, (3) failure to utilize copper, or (4) an excessive rate of loss of copper from the body. None of these conditions has been described in human subjects,[27] unless the patients described by Sturgeon and Brubaker,[7] Lahey,[9] and others [1-5] and the two patients (Cases 1 and 2) described in this report represent mild dietary deficiencies of copper.

Hypocupremia as a result of inability to synthesize apoceruloplasmin (I, B) has been described in normal newborn infants [28] and in patients with Wilson's disease.[29] Lahey [9] mentions that children with kwashiorkor and severe hypoproteinemia have been found to have copper levels between 43μg. and 86μg/100 ml. The situation in these children may be analogous to the hypocupremia observed in swine fed a low-protein diet.[25] In collaboration with Major C. E. Butterworth,[30] we have observed hypocupremia in a few patients with tropical sprue and hypoproteinemia. In these patients the hypocupremia failed to respond to the administration of copper. Detailed studies in celiac disease are not available, but Axtrup [1] observed a serum copper level of 61μg/100 ml. in a single patient, and Lahey studied two infants with "chronic enteritis" associated with edema and hypoproteinemia and found values of 12μg. and 26μg/100 ml. We have observed one adult patient with chronic 'idiopathic hypoproteinemia" with a serum copper concentration of 60μg/100 ml.[31]

Hypocupremia due to excessive loss of ceruloplasmin in the urine (II, A) has been observed in patients with the nephrotic syndrome.[12,32] Conceivably, hypocupremia could also result from loss of ceruloplasmin through extensive serous discharge such as follows burns or through excretion into the gastrointestinal tract. Such conditions have not been reported. Hypocupremia due to an accelerated rate of catabolism of ceruloplasmin has not been demonstrated clearly. However, as discussed above, the hypocupremia in infants with "transient dysproteinemia" [26] may be due to this cause.

The above classification of hypocupremia must be considered as tentative. Further studies are needed in patients with kwashiorkor, sprue, celiac disease, and idiopathic hypoproteinemia.

Summary and Conclusions

Two infants are described with severe microcytic hypochromic anemia, hypoalbuminemia, hypoferremia, and hypocupremia. There was a prompt hematologic response and an appreciable increase in serum albumin following the parenteral administration of iron. The serum copper level was restored to normal only after the administration of copper. It is suggested that the hypocupremia in these two infants was due to a depletion of copper. The explanation for this depletion of copper is obscure.

A third infant with mild normocytic anemia, severe hypoalbuminemia, hypoglobulinemia, hypoferremia, hypocupremia, and hypocalcemia was studied. The administration of copper to this patient was not

followed by a significant increase in serum copper. Recovery occurred slowly and was probably spontaneous and not related to therapy with iron or copper. It is suggested that the hypocupremia in this infant was not due to depletion of copper but was caused either by failure to synthesize apoceruloplasmin or by an increased rate of destruction or loss of this protein from the body.

The various causes of hypocupremia in infants and children are discussed, and a tentative classification is proposed.

Miss Doris Kurth and Mrs. Marilyn Dahm gave technical assistance. Mr. J. K. Horner, Kennecott Research Center, determined the copper concentration of the iron-dextran preparation for us. The iron-dextran preparation (Imferon) was supplied by Dr. H. M. Leyland of the Lakeside Laboratories, Milwaukee, Wis.

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Use of Tranquilizers for Mentally Deficient Patients

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In a recent article by Tarjan et al.[1] the use of chlorpromazine in mentally deficient patients was reviewed, possible complications from its use were well outlined, and the need for a double-blind research study to measure its objective effectiveness was indicated.

Timberlake et al.[2] reported a double-blind study on the effects of reserpine on 200 mentally retarded children. These authors felt that the two-month period of treatment with the drug followed by two-months' use of a placebo was "too brief to determine how well improvement will be sustained."[2] They did not attempt to compare the effectiveness of chlorpromazine with that of reserpine. The comparative drug study by Sprogis et al.[3] did not utilize the double-blind technique but did suggest that, while reserpine appeared more effective initially, chlorpromazine appeared to have a more-lasting effect after the drugs had been withdrawn. They suggested the use of a combination of these two drugs.

This paper is the description of a double-blind study of 40 mentally deficient patients, comparing the effectiveness of chlorpromazine, reserpine, the combination of these two drugs, and a placebo on the behavior of low-grade mentally deficient children.

Method

Forty patients of the Austin State School, who presented the severest management problems, were selected for this study. They were then divided into four approximately matched groups (Table 1) by sex, age, weight, ward placement, mental-age function, etiology, and degree of baseline management problem. The behavior problems included severe self-mutilation, such as biting, slapping, gouging one's eyes, digging at rectum, or pulling out hair; tension-reducing behavior, such as rocking, smearing of faces, masturbation, and head banging, and assaultive or aggressive attacks on other children and staff.

The age of the selected subjects in each group, as shown in Table 1, ranged from 8 to 40 years; mental functioning, from approximately 12 months to 6 or 7 years, with eight or nine females to one male and a fairly equitable distribution of basic etiology in each of the four matched groups.

From January, 1955, into February, 1956, or through 380 days, these 40 cases were rotated through each one of four experimental conditions referred to as W, X, Y, and Z. Each of these letters represented capsules prepared to look alike and to contain unit dosages of the following drugs: reserpine 0.5 mg., chlorpromazine 50 mg., combination reserpine and chlorpromazine 0.25 mg. and 25 mg., respectively, and placebo, an inert chemical compound.* The key to the identity of these drugs was kept by the drug firm until the study was completed. Consequently, no one working on the study knew the composition of the similar-appearing capsules.

Objective Recording of Behavior.—The effects of the drugs were recorded by child-care workers on the wards during all three shifts. A behavior check list was prepared in which the total behavior of the child was broken down into separate behavior items. Care was taken to list particularly all the behavior items which constituted a problem in management. The instructions were to put an X by any one of the items which applied during the eight-hour shift, and three charts were made for each child during a 24-hour period.

Collaboration or discussion between recording staff from each shift was recognized with the group as undesirable and sufficient to disqualify the accuracy of the study. It is interesting to note that the interscorer reliability of the check lists was determined to be of the order of 0.75 to 0.85 on occasions in which three attendants were asked

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*All capsules were prepared and supplied by Smith, Kline & French Laboratories.

TABLE 1.—*Data on Four Experimental Groups*

Case No.	Sex	Age	Mental Age	Probable Etiology	Baseline Behavior
101	F	12	1-0	Familial	Bangs, rocks, smears
102	F	17	2-0	Familial	Slaps, strikes others
103	F	13	1-2	Meningitis	Rocks, digs, bites, smears
104	F	14	6-0	Cong. maldv.	Slaps, bites, destroys
105	F	45	2-0	Org. brain dis.	Slaps, bites, destroys
106	F	21	1-0	Cereb. inf. (measles)	Bangs, bites, slaps
107	F	36	4-0	Cereb. trauma (labor)	Digs, tension-reducing behavior
108	M	9	2-0	Cong. maldv.	Slaps, bites, restless
109	M	11	1-9	Cereb. trauma (labor)	Bangs, bites
110	F	8	1-0	Cereb. inf. (epi. enc.)	Bangs, slaps, bites
201	F	16	1-6	Cereb. inf. (pertussis)	Slaps, bites, tears
202	F	13	5-6	Cereb. inf. (pertussis)	Slaps, bites, tears
203	F	17	1-2	Familial	Bangs, slaps, bites
204	F	14	1-9	Familial	Slaps, tears, rubs eyes
205	F	40	1-0	Schilder's disease	Rocks, slaps, bites
206	F	25	1-0	Cong. maldv.	Bangs, digs, bites, slaps
207	M	11	1-6	Cereb. trauma (labor)	Bites, slaps
208	M	8	1-6	Cong. maldv.	Slaps, bites, restless
209	M	11	1-6	Cong. maldv.	Bangs, slaps self
210	F	10	1-0	Schilder's disease	Slaps, bites
301	F	13	1-3	Epidemic enc.	Bangs, rocks, digs
302	F	12	1-6	Familial	Digs, bites, tension-reducing
303	F	14	1-9	Cereb. trauma (labor)	Digs, bites
304	F	17	2-0	Cong. maldv.	Rocks, digs, slaps
305	F	41	7-6	Cereb. trauma (labor)	Slaps, bites
306	F	32	4-9	Schizophrenia, chronic	Delusional, screams, tears
307	F	28	6-0	Familial	Slaps, tears, cusses
308	M	22	6-0	Cereb. inf. (measles)	Digs, slaps, bites, tears
309	F	26	1-0	Cereb. inf. (measles)	Digs, slaps, bites
310	F	7	2-6	Cereb. trauma (labor)	Slaps, tears
401	F	14	3-0	Cereb. trauma (labor)	Digs, bites
402	F	12	4-6	Organic brain disease	Bangs, digs, slaps
403	F	13	4-0	Cereb. inf. (epi. enc.)	Slaps, bites, tears
404	F	14	-6	Cereb. trauma (labor)	Digs, tension-reducing
405	F	42	3-3	Mongolism	Rocks, digs
406	F	21	1-6	Cong. maldv.	Bangs, rocks, slaps
407	F	24	1-0	Phenylpyruvic acid Oligophrenia	Bangs, rocks, digs
408	F	8	1-6	Cong. maldv.	Digs, slaps
409	F	11	1-0	Cong. maldv.	Bangs, digs, slaps
410	M	11	1-2	Familial	Digs, slaps, bites

to fill out the behavior check list for the same subjects.

Data from all of the daily behavior charts were recorded on IBM cards and were subsequently analyzed.

Clinical Findings

Observations from this study are recorded in terms of clinical and statistical findings. Table 3 outlines the percentage of group improvement in response to each of the experimental conditions. All four groups showed an improvement of 80% to 100% on chlorpromazine, 70% to 100% on reserpine, and 70% to 90% on a combination of these drugs. None of the children who failed to show improvement on chlorpromazine responded more favorably to a combination of the drugs. Only two of the children who did not respond to chlorpromazine showed a favorable response to reserpine. These children were of the familial (endogenous) primary amentia type. Four children who did not respond favorably to reserpine did respond to chlorpromazine; three of these were children with postinfectious encephalitic processes,

TABLE 2.—*Double-Blind Design* *

Group	Baseline (28 Days)	Cond. 1 (60 Days)	P (28 Days)	Cond. 2 (60 Days)	P (28 Days)	Cond. 3 (60 Days)	P (28 Days)	Cond. 4 (60 Days)	P (28 Days)
I	--	W	--	Z	--	Y	--	X	--
II	--	X	--	W	--	Z	--	Y	--
III	--	Y	--	X	--	W	--	Z	--
IV	--	Z	--	Y	--	X	--	W	--

* W, X, Y, and Z refer to capsules, as described in the text. I, II, III, and IV refer to population groups, as described in the text. P indicates a 28-day placebo period. None of staff (except nonparticipating senior author) knew the frequency of placebo periods. Condition 1 refers to the initial 60 days, when each matched group received one of the "unknown" capsules, dosage determined by age, weight, and individual tolerance extending from 6 unit capsules per day for younger patients up to maximum of 10 units per day for older and heavier patients. Conditions 2, 3, and 4 represent 60 days each, when Capsule W, X, Y, or Z was given. Final P provided a 28-day period during which psychometric and social maturity studies on all subjects were reevaluated.

TABLE 3.—*Percentage of Subjects in Each Group Showing Improvement*

Group	Subjects Showing Improvement, %			
	Chlorpromazine	Reserpine	Combination	Placebo
I	90	70	80	50
II	100	100	90	70
III	80	80	70	60
IV	90	90	90	40

and one was retarded as a result of cerebral trauma during labor and delivery.

Perhaps the most interesting finding in this study was the high incidence of improvement with use of the placebo, ranging from 40% to 70%. This placebo suggestion effect is of such significance as to raise serious doubts about conclusions as to the effect of medication on mentally deficient patients unless these medications are studied through the use of a double-blind research design, as outlined in this presentation. For example, the subjects in Group IV, who received the placebo first, showed an 80% improvement through more than half of the experimental period and then their behavior reverted to baseline type during the last two or three weeks of that experimental period. This pointed to the need for at least an eight-week observation on drugs and suggested that in any period of less than eight weeks the subjects may well be responding to the placebo effect.

An attempt was made to determine clinical responses to medication in terms of etiology of the mental deficiency (Table 4).

The number of cases falling into each classification of etiology is not a large enough sample for the study to be significant in terms of specific response according to etiology.

Statistical Findings

In the first eight weeks of the study all groups, including the placebo group, showed a statistically significant (with use of the χ^2-test to determine changes in the frequency of improvement of behavior categories) increase in the number of behavior categories showing improvement.

In each of these first three groups improvement due to drugs reached a peak during the seventh week, suggesting that eight weeks was long enough to demonstrate maximum drug effect. In every case, group data indicated a leveling off of the number of improved categories during the seventh and eighth weeks. Also, when the drugs were withdrawn the decrease in the number of improved categories during the placebo period (9th to 12th weeks) for Groups I, II, and III is statistically significant, with use of χ^2-test.

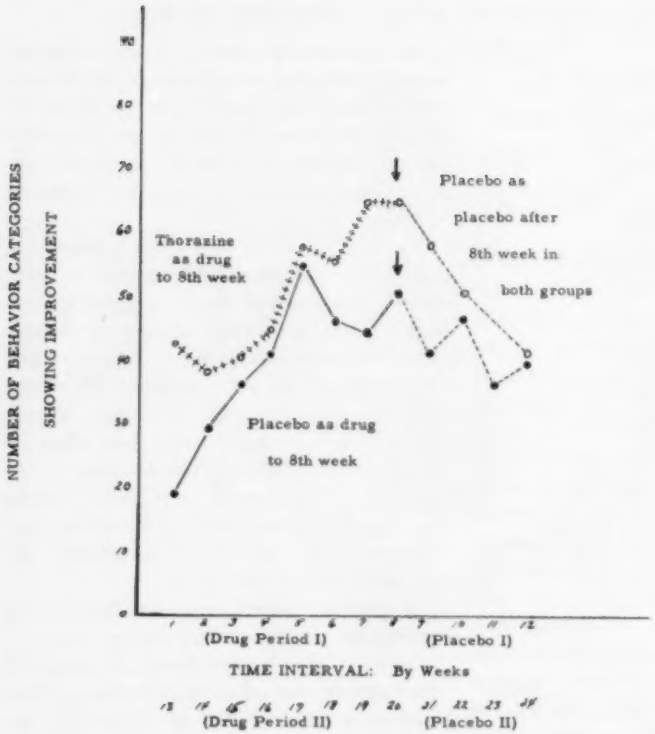
Statistical analysis suggested that while a significant amount of improvement occurred in Group IV (placebo group) the shape of the curve leveled off at the 5th week and the decline in the number of improved categories during the 9th to 12th weeks is not statistically significant. Thus, the characteristic rise and fall in improvement of the first three groups does not occur in the placebo group, even though the relative amount of improvement due to the "placebo suggestion effect" is significant statistically.

The Figure compares this placebo effect in Group IV during the first period with improvement in Group IV taking chlorpromazine during the second period.

The quantitative expression of improvement utilized here is relative and not absolute. Because behavior was assessed in

TABLE 4.—*Improvement According to Etiology*

Etiology	Chlorpromazine		Reserpine		Combination		Placebo	
	Imp.	None	Imp.	None	Imp.	None	Imp.	None
Familial (Primary amentia)	5	2	7	0	4	3	3	4
Cong. maldv.	8	1	8	1	9	2	6	3
Cereb. trauma	8	0	7	1	7	1	4	4
Post. infec.	8	1	6	3	9	0	5	4
Undiagnosed	2	1	2	1	2	1	0	3
Schilder's dis.	2	0	2	0	2	0	2	0
Phenylpruvic acid oligophrenia	1	0	1	0	1	0	0	1
Mongolism	1	0	1	0	1	0	1	0


NUMBER OF BEHAVIOR CATEGORIES
SHOWING IMPROVEMENT
Thorazine as drug to 8th week
Placebo as drug to 8th week
Placebo as placebo after 8th week in both groups
(Drug Period I)
(Placebo I)
TIME INTERVAL: By Weeks
(Drug Period II)
(Placebo II)

Group IV. — Placebo suggestion effect (first period) and chlorpromazine (Thorazine) response (second period).

terms of relative improvement with reference to the person's own previous behavior, there is some limitation placed upon quantitative comparison of the results from group to group. However, during the first 12 weeks Group III (chlorpromazine) evidenced much greater improvement than the other three groups. Group II (combination) came next in order of improvement.

Statistical findings during the second 12-week period were far less clear-cut as evidence indicating distinct rises and falls in improvement corresponding to the giving or not giving of medication. This fluctuation in behavior was probably due to a combination of several factors, such as persistence of some drug effect from the previous period, persistence of improved behavior beyond the drug period, and progressive changes taking place in the person during the six-month period aside from the drug effects.

The results recorded for Group IV (chlorpromazine) during the second 12-week period are, however, statistically striking for several reasons (Figure).

There was a clear-cut increase of improved behavior.

This improved behavior reached a peak during the seventh to eighth weeks of treatment with the drug, just as it did with the first three groups during the initial drug period.

The latter finding suggests that this initial response to the drugs is distinctive and that a characteristic rise and fall in improvement does occur very much as is described by the data.

This increase in improved behavior occurred over and above the placebo effect noted during the first three months, as a significant gain in itself.

Since the curve of Group IV showed a statistically significant increase during the

eight weeks of drug therapy, one can point with greater confidence to the behavior fluctuations of the other two drugs as being not merely artifacts of the method of collection but as being truly representative of what actually occurred.

Complications

The following side-effects seem significant in our study.

Drowsiness occurred in 40% to 50%, as we attempted to increase the dose to the point of producing drowsiness and then to decrease it by 1 unit capsule per day.

Hypotensive symptoms of giddiness or syncope occurred in only 10% to 15% as early as the third or fourth day (probably chlorpromazine activity), sometimes during the second week (thought to be due to reserpine).

Coryza and influenza symptoms were observed in 30%.

Gastrointestinal symptoms of transient diarrhea or occasional constipation occurred in less than 5%.

Photosensitivity or exaggerated sunburn effect occurred in less than 5%.

Parkinson-like drooling, tremor, and rigid posturing were observed in only one patient, a 32-year-old woman.

Grand mal seizure occurred in one patient without a previously known seizure history and in one patient with known seizures.

Other side-effects described in the literature but not observed in our study include stomatitis when chlorpromazine is chewed in the mouth, leukopenia, and transient extrahepatic biliary obstruction, said to occur in less than 1% of the cases receiving chlorpromazine.

One of us (W. C. A.) has since observed shifts in differential WBC from the polymorphonuclear to the lymphocyte series in a small number of children receiving either chlorpromazine or reserpine. It appears that differential cell counts should be done every six to eight weeks for all children receiving the tranquilizing drugs, until it is certain what effect prolonged medication has on the hematopoietic system.

Comment

This double-blind study strongly confirms the clinical impressions outlined by Tarjan.[1] Chlorpromazine does appear to be an effective drug, and a predictable one, in reducing severe self-mutilation, tension-reducing behavior, and assaultive or aggressive acting-out behavior in a large majority of low-grade mentally deficient patients. Neither reserpine nor a combination of reserpine and chlorpromazine showed any more effectiveness in treating this population. Yet it should be restated that the tranquilizing drugs, in themselves, are not a panacea to the problem. They did seem to decrease some of the natural counter-hostility which attendants sometimes feel toward very low-grade children who are severe management problems. By decreasing the severity of the patient's problem and by increasing the patient's response to ward management and care given by child-care workers or attendants, the over-all ward environment was substantially improved. None of these drugs singly or in combination increased either the intelligence or the social maturity of any of the patients in this study, as reported by Bair et al.[4] We would repeat Tarjan's statement with reference to chlorpromazine: "Where hyperactivity or withdrawal, however, interfered with the testing process, at times its administration, through beneficial effects on secondary symptoms, substantially improved the numerical score obtained on intelligence tests."[1]

Summary

Forty low-grade mentally deficient patients with severe behavior and management problems were included in a double-blind study comparing the effectiveness of chlorpromazine, reserpine, the combination of these two drugs, and a placebo in changing their behavior. The study extended over a period of 380 days. Four approximately

matched groups of selected subjects were rotated through four experimental conditions for 60 days each, with a 28-day placebo period between medications. Drug dosage ranged from 3 mg. to 5 mg. per day for reserpine, 300 mg. to 500 mg. per day for chlorpromazine, and 1.5 mg. to 2.5 mg. of reserpine in combination with 150 mg. to 250 mg. of chlorpromazine. The age of the subjects ranged from 8 years to 40 years.

Child-care workers on the wards were trained in recording observations on a daily behavior check list for three shifts covering a 24 hour period. Interscorer reliability of check lists was of the order of 0.75 to 0.85.

The percentage of subjects in each of the four groups showed clinical improvement from 80% to 100% with chlorpromazine, 70% to 100% with reserpine, and 70% to 90% with a combination of these drugs.

A placebo effect ranging from 40% to 70% improvement demonstrated the need for a placebo control group in all research designs concerned with effectiveness of drugs on behavior. This effect seemed to persist up to six weeks, and a period of eight weeks of receiving a specific drug is believed to be minimal for reliable observations on these subjects.

Standardized psychometric and social maturity testing before and after periods of medication did not indicate significant changes in intellectual or social functioning in these selected subjects.

Drowsiness in 40% to 50% of the subjects was the only major complication.

Grand mal seizures occurred in one patient not previously known to have seizures and in one patient with known seizures.

White blood cell and differential counts should be done every six to eight weeks for children receiving tranquilizing drugs.

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The Use of Hydrocortisone in the Treatment of Tuberculous Meningitis

A Study of Steroid Concentrations in Cerebrospinal Fluid

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Therapy of tuberculous meningitis presents the problem of controlling the tuberculous infection without causing serious or permanent damage to the patient due to the undesirable side-effects of certain of the antituberculous drugs. The combined use of streptomycin, aminosalicylic acid (PAS), isoniazid (isonicotinic acid hydrazide, INAH), and hydrocortisone has changed dramatically the once-hopeless outlook in this disease.[1]

In the original clinical studies hydrocortisone was administered intrathecally; however, during the last two or three years intrathecal therapy has been abandoned generally as being unnecessary.[1-3] Yet, although clinical evidence suggested that orally or intramuscularly administered hydrocortisone was passing into the cerebrospinal fluid, no reported measurements of 17-hydroxycorticosteroid levels in the cerebrospinal fluid of patients receiving oral or intramuscular hydrocortisone therapy could be found in the literature. Therefore, it was decided to determine whether steroids, as indicated by Porter-Silber chromogens, were present in the cerebrospinal fluid of patients four hours after the oral or intramuscular administration of hydrocortisone.

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This investigation was supported in part by research Grant RG 5173 from the National Advisory Health Council, Public Health Service.

From the Department of Pediatrics, University of Utah School of Medicine. This work was done during the tenure of an American Heart Association Fellowship (Dr. Cranny).

Methods and Materials

The Reddy modification of the Reddy-Jenkins-Thorn technique[4] was used to determine the levels of 17-hydroxycorticosteroids (17,21-dihydroxy-20-ketosteroids) in several samples of spinal fluid taken four hours after the administration of hydrocortisone either orally or intramuscularly. As a control, the 17-hydroxycorticosteroids (17-OHCS) were determined similarly in three random samples of normal spinal fluid and in two samples of spinal fluid obtained from children who had received hydrocortisone intravenously. In addition, 100μg. of PAS and 100μg. of isoniazid were extracted from water and subjected to the reagents employed in the Reddy-Jenkins-Thorn procedure to determine whether these drugs might produce false-positive values for steroids.

Results

As can be seen in Table 1, there was an extremely small amount of detectable Porter-Silber chromogens in the normal control spinal fluid samples. There were, however, 17-OHCS in all of the samples from the patient with tuberculous meningitis who was studied (Table 2), and 17-OHCS were easily detected in two children, without tuberculous meningitis, two and four hours after the intravenous administration of hydrocortisone for half-life studies (Table 3). In the drug control samples (Table 4), consisting of distilled

TABLE 1.—*17-OHCS Levels in Normal Spinal Fluid*

Patient	Spinal Fluid 17-OHCS, μg. %	Remarks
1	2.4	Adult
2	0.71	Child
3	0.86	Child

TABLE 2.—*17-OHCS Levels in Spinal Fluid of Patient with Tuberculous Meningitis* *

	Steroid Therapy	Plasma 17-OHCS, μg. %	Spinal Fluid 17-OHCS, μg. %	Remarks
6/21/57	Hydrocortisone, 100 mg/day, i. m.			
6/22/57	Hydrocortisone, 100 mg/day, i. m.	4.6		
			3.0	Chloroform-extracted; Nelson Samuels technique
7/15/57	Hydrocortisone, 20 mg. 5 times a day, p. o.	6.9		
			18.0	Same spinal fluid reextracted with butanol; Reddy-Jenkins-Thorn technique
8/5/57	Hydrocortisone, 75 mg. t. i. d., p. o.		71.2	
8/12/57	Hydrocortisone, 75 mg. t. i. d., p. o.		41.3	
8/19/57	Hydrocortisone, 75 mg. t. i. d., p. o.		18.5	
8/28/57	Hydrocortisone, 100 mg/day		20.0	
10/30/57	None since 10/1/57		14.0	
12/12/57	None		17.0	
1/21/58	None		0.0	

* All determinations calculated as micrograms per millimeter of cerebrospinal fluid and corrected to micrograms per cent.

water to which was added 100μg. of either PAS or isoniazid, Porter-Silber chromogens were not detected.

The following is a brief case report.

A 3-year-old white girl was admitted to the Salt Lake County General Hospital on June 18, 1957. She had been well until one month prior to admission when she experienced the gradual development of malaise, irritability, and fever, followed in one week by vomiting. One week later the vomiting had increased and the intake had become poor. Anisocoria and nuchal rigidity were noted, and a lumbar spinal puncture yielded fluid with 150 leukocytes per cubic millimeter (80% lymphocytes), 108 mg. % of protein, and a pressure of 300 mm. of water. Penicillin, chloramphenicol (Chloromycetin), and sulfonamide were given for one week, with no clinical improvement. A repeat lumbar puncture revealed 208 leukocytes, most of which were "lymphocytes," 150 mg. % protein and a pressure of 300 mm. of water. The patient was then referred to the Department of Pediatrics, the University of Utah. No family history of tuberculosis was found, despite repeated questioning by several examiners.

The patient was a well-developed well-nourished white girl, who appeared to be the stated age. She was acutely and perhaps chronically ill, was irritable, and varied in her response from cooperative to uncooperative. The right pupil was larger than the left. Bilateral papilledema, moderate nuchal resistance, and bilateral unsustained ankle clonus were noted. The patellar reflexes were hyperactive, whereas the remaining deep tendon reflexes were normal or diminished.

A chest film revealed an acute inflammatory infiltrate in the right upper lobe. In skull films separation of sutures and an increase in the digital markings could be seen. On the day after admission a generalized grand mal seizure occurred, and a few hours later bradycardia (rate of 20 per minute) and respiratory slowing developed. The respiratory rate declined to 6 per minute, with occasional apnea. First strength P. P. D. was negative at 48 hours.

The following day a younger sibling was seen by us because of leg pain and was found to have x-ray evidence of gross pulmonary miliary tuberculosis. Further questioning of the family revealed extensive active and fatal tuberculosis in the family, and on a chest film of the father signs of open cavitational pulmonary tuberculosis could be seen.

Our previous suspicion of tuberculous meningitis being thus strengthened, immediate cranial decompression, by trephining, followed by treat-

TABLE 3.—*17-OHCS Levels in Spinal Fluid During Hydrocortisone Half-Life Studies*

Control Subject	Plasma 17-OHCS Time *	Plasma 17-OHCS μg. %	Spinal Fluid 17-OHCS, μg. %	Remarks
1 (miliary tuberculosis; mild clinical illness)	Control	9.3	--	Age 4 yr.; received hydrocortisone, 1.0 mg/kg., i. v., for half-life study; spinal fluid obtained 4 hr. after injection was completed
	30	68.5	--	
	60	58.6	--	
	90	35.2	--	
	120	35.8	--	
	240	--	14.0	
2	Control	18.8	--	Age 4 yr.; received hydrocortisone 1.0 mg/kg., i. v., for half-life study; spinal fluid obtained 2 hr. after injection was completed
	30	99.1	--	
	60	48.9	--	
	90	56.6	--	
	120	52.9	69.0	
	180	35.4	--	

* Minutes after completion of the intravenous administration of hydrocortisone.

TABLE 4.—*Drug Control*

Drug	Technique	Porter-Silber Chromogens
Isoniazid	100 μg. dissolved on 10 ml. of distilled water and subjected to Reddy-Jenkins-Thorn procedure *	0.0
Sodium aminosalicylate	Same	0.0

ment with streptomycin, isoniazid, PAS, and hydrocortisone was accomplished (June 21, 1957).

At the time of the operation it was not possible to measure the ventricular fluid pressure, but it was "extremely high." Spinal fluid pressure was 285 mm. of water initially and gradually declined to 150 mm. of water. The neurosurgeon felt certain that a partial block existed.

P. P. D. No. 2 was strongly positive. After the decompression the patient's condition improved, and after several days it was nearly normal. Streptomycin was discontinued after one month. Hydrocortisone, 100 mg. per day, was given for two months and was then gradually decreased in amount during the next month, at which time it was discontinued (Oct. 1, 1957). At this writing almost all the side-effects of hydrocortisone have disappeared.

All bacteriologic studies on spinal fluid, sputum, and gastric washings were negative for tubercle bacilli. Spinal fluid on Oct. 30, 1957, was clear; pressure was normal, and 3 leukocytes per cubic millimeter were seen.

Comment

With the demonstration by Ragan et al.[5] that cortisone caused a delay in development of all elements of connective tissue in rabbit ear skin wounds, the prevention of the formation of the fibrinous exudate that it characteristic of tuberculous meningitis seemed possible. Subsequent studies by Spain et al.[6] on the effects of simultaneous administration of cortisone and streptomycin to guinea pigs which were infected with tuberculosis demonstrated that if the dose of streptomycin was high enough the tuberculous involvement of the animals at autopsy was lessened whether they had received cortisone or not. Soon thereafter Karlson et al.[7] found that streptomycin, when given simultaneously with cortisone, afforded little or no protection against spread of the disease; however, in this latter study the doses of drugs used were less than half those of Spain et al.[6] Vigorous condemnation of the use of cortisone in the treatment of tuberculosis was rapidly forthcoming,[8-12] and, although the evidence was all indirect or inferential, a cautious attitude was justified. Although the theoretical benefits of cortisone in the treatment of tuberculous meningitis were recognized previously,[13] the development of new antituberculous drugs enabled investigators to prevent the systemic spread of tuberculosis while giving the patient any advantage that cortisone therapy might offer. With this advance came the realization that cortisone could be used safely and beneficially in the treatment of tuberculous meningitis, provided adequate amounts of effective antituberculous drugs were administered simultaneously.[1-3,14,15] The fact that orally or intramuscularly administered hydrocortisone is detectable in substantial amounts in the cerebrospinal fluid within four hours after an administered dose was demonstrated in the patient with tuberculous meningitis reported in this paper and in two other patients without tuberculous meningitis on whom hydrocortisone half-life studies were being done.

An interesting but unexplained observation was the finding of a high 17-OHCS concentration in the spinal fluid of the patient with tuberculous meningitis two and one-half months after hydrocortisone therapy had been discontinued. One could speculate that this may have been due to a continued release of steroids that had accumulated in the tissues, thus maintaining a high blood and spinal fluid 17-OHCS concentration. Also, it may be that the permeability to steroids of the "blood-brain barrier" is increased during the acute and convalescent stages of certain diseases. Whether one or both of these factors might be operative here cannot be determined on the basis of present data. In this regard, it would be interesting to know what the 17-OHCS spinal fluid levels are in patients with Cushing's disease or in patients receiving steroid therapy for diseases other than meningitis.

Summary

17-Hydroxycorticosteroids were demonstrated in the cerebrospinal fluid of a patient suffering from severe tuberculous meningitis after hydrocortisone had been admin-

istered orally, intramuscularly, or by both routes.

In this patient no evidence of spread of tuberculosis induced by the hydrocortisone was noted.

17-Hydroxycorticosteroids were found to be present in extremely small amounts in normal cerebrospinal fluid.

One hundred micrograms of aminosalicylic acid and of isoniazid did not cause a positive Porter-Silber reaction.

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Dietary and Storage Factors in Iron-Deficiency Anemia of Infancy

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With the Technical Assistance of Frances DeLuca, B.S., and Alice Manchester, B.S.

Several factors are thought to contribute to the iron-deficiency anemia of infancy. Included among these are decreased dietary iron, inadequate iron stores at birth, and excessively rapid growth. This study was undertaken to evaluate the relative importance of these factors.

Methods and Materials

The peripheral blood was studied in all infants, as previously described,[1] with the exception of some hemoglobin determinations, which were measured with use of a modification of the cyanomethemoglobin method.[2] Serum iron and iron-binding capacity were measured by the method of Peters et al.[3,4] as modified from the Barkan and Walker procedure.[5]

Seventy-seven infants with iron-deficiency anemia were studied during the years 1954 to 1956. The general physical condition of the infants was evaluated. Where possible, careful histories were taken, with special reference to age, sex, race, birth weight, present weight, diet, and blood loss. Inquiries were also made into maternal history of anemia, iron therapy during pregnancy, and blood loss.

Results

All infants exhibited a hypochromic microcytic anemia. Hemoglobin concentrations ranged from 2.5 gm. % to 9.3 gm. %, with an average of 6.3 gm. Hematocrit values, measured in 42 infants, ranged from 11% to 35%, with an average of 24.8% (Fig. 1). The serum iron was measured in 35 infants (Fig. 2). The highest value was 48μg. %, well below our lowest normal value in adults and also significantly lower than the values Sturgeon[6] found in normal infants of a comparable age group. The serum iron-binding

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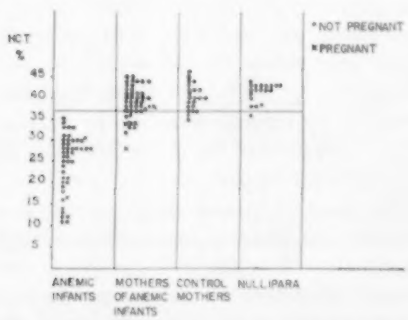

Fig. 1.—Distribution of hematocrit values of anemic infants, mothers of anemic infants, control mothers, and nulliparae. Horizontal line represents a hematocrit value of 36%, the lower limits of normal in our series.

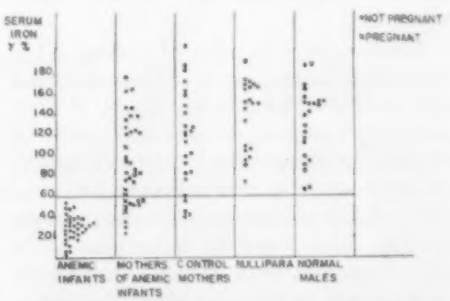

Fig. 2.—Distribution of serum iron values of anemic infants, mothers of anemic infants, control mothers, nulliparae, and normal males. Horizontal line represents a serum iron of 60μg. %, the lower limits of normal in our series.

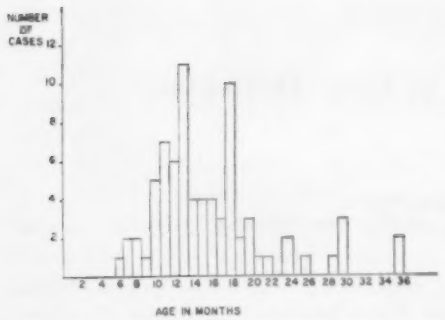

Fig. 3.—Age distribution by month of iron-deficient infants. The majority of cases occurred between the ages of 10 and 20 months.

capacity was normal or elevated in all but three cases. In these, an active infection was present and the serum iron-binding capacity was below 300μg. %. All three responded to iron therapy. The average value in 27 noninfected patients was 415μg. %. Stools were tested for occult blood in 13 cases. In only one of these was the stool positive for blood, at which time the patient had shigellosis.

The average age of the infants was 15.7 months, with a range from 7 to 36 months. In Figure 3 it can be seen that the majority of cases occurred between the ages of 10 and 20 months. Fifty of the anemic infants were boys, and twenty-seven were girls. This predominance of boys was not seen in the control hospital population of the same age group, in which the ratio was 19 boys to 16 girls. The preponderance of boys was not correlated with race or low birth weight.

There were four pairs of siblings other than twins in our series and an additional two cases in which a family history of iron-deficiency anemia in siblings could be elicited. All except one child were Negroes; the one exception was a Puerto Rican infant. There was no evidence that younger siblings were found to be anemic at an earlier age than older siblings. Prematurity was present in only one pair of siblings, and these two children were also both severely malnourished. In addition, there were five twins in our series, all of whom were premature by dates and weighed less than 5½ lb. at birth.

There were approximately equal numbers of white and Negro infants (36 white and 39 Negro patients). This distribution is not typical of the hospital pediatric population, of which 70% are Caucasian. To determine whether the increased incidence of Negroes in our series was due to the greater frequency of low birth weights in this racial group,[7-9] birth weights were correlated with race. There were 14 of 33 Negro infants who weighed less than 5 lb. 8 oz. at birth, as compared with 10 of 31 white infants. These figures revealed no significant difference between the incidences of low birth weights in the two races.

Patients were divided into two categories according to birth weight, 5 lb. 8 oz. being used as the dividing line. In 43 cases the birth weight was greater than this. Twenty-five infants weighed less, and, of these, thirteen were known to be more than three weeks premature by dates. The birth weight of nine infants was not known. The frequency of prematurity is significantly different from that in a control group of 25 infants, only 2 of whom had low birth weights.

The weights of 26 full-term boys and 9 full-term girls were plotted on standard growth charts (Fig. 4) in an effort to evaluate the importance of excessive weight increment as a factor contributing to iron-deficiency anemia. In only three patients were the weights above the 97th percentile. Eight were below the 3d percentile, and twenty-one, or 65%, fell below the 25th percentile in weight. None of the 25 premature infants was above the 97th and 10 fell below the 3d percentile.

The standard growth charts do not give adequate information concerning growth increments when the birth weight is abnormal. Therefore, to evaluate growth rate in these patients, the factor by which the birth weight had multiplied at the time of study is compared with the expected growth-rate curve (Fig. 5). Normal full-

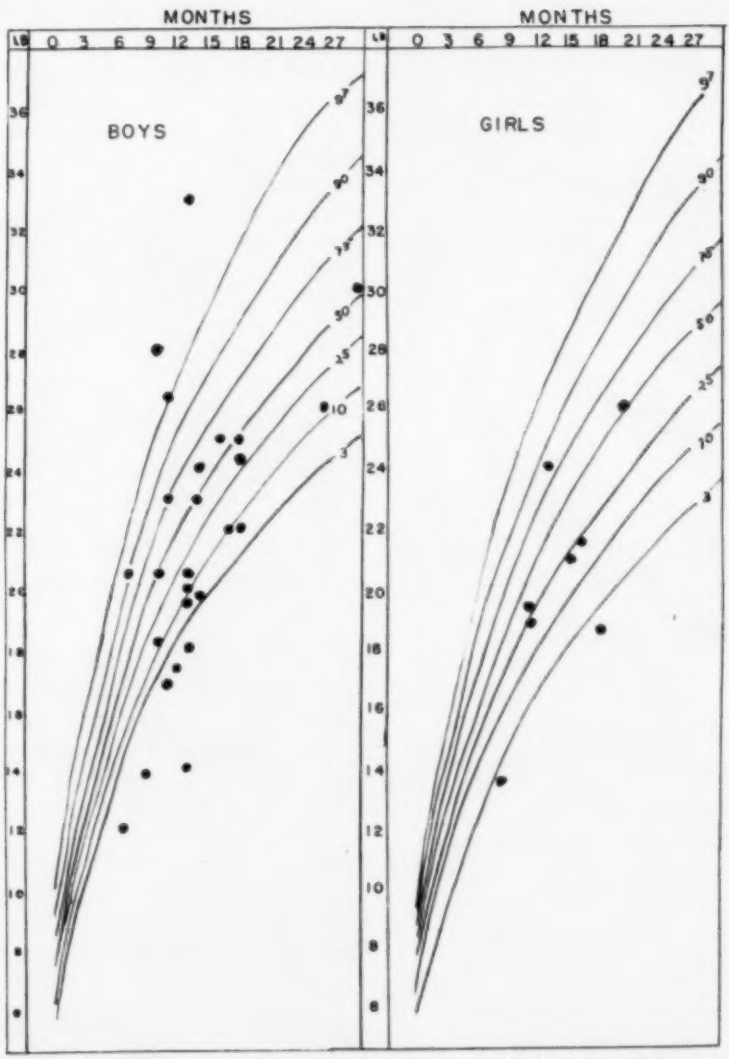

Fig. 4.—Weight distribution by age of iron-deficient infants, exclusive of premature infants, plotted on growth percentile charts. The curved lines represent weight percentiles. The majority of infants are below the 25th percentile by weight.

term infants will double their birth weight at 5 months, triple it at 1 year, and quadruple it at 2½ years.[10] Only 3 of 26 full-term infants, as opposed to 13 of 17 premature infants, were more than 0.5 over the expected growth factor for their age. Two premature infants showed astoundingly high growth increments, the factors being 14.7 and 16.7 at the age of 19 months.

Since the supply of iron at birth depends not only on the size of the infants but also on the availability of maternal iron, the mothers of these infants were studied. Maternal ages varied from 16 to 43 years at the time of delivery. There was a wide distribution through the child-bearing age. Sixty-nine per cent of the mothers of anemic infants had had three or more preg-

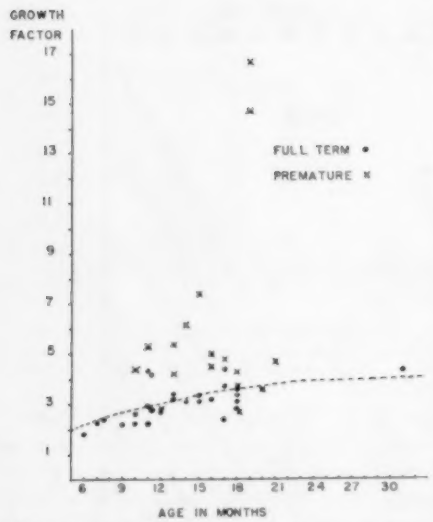

Fig. 5.—Growth factor of full-term and premature iron-deficient infants plotted according to age. "Growth factor" is defined as present weight divided by birth weight. The dotted curve represents the expected values. The majority of premature infants showed high growth factors. This finding was uncommon in full-term infants.

nancies, as compared with 75% of the mothers of nonanemic infants on the wards, and there was no significant difference in the distribution of number of pregnancies between the two groups of mothers. Fourteen mothers stated that they took iron while pregnant with the patient under study. Fifteen did not receive any iron therapy. In the remainder this fact could not be accurately determined.

Hematological studies were performed on certain of the mothers and suitable controls. In the absence of other disease, the serum iron is an accurate reflection of iron stores, and it therefore has been considered as the most reliable evidence of iron deficiency in this group. Serum iron values were measured in 40 mothers of anemic infants. Of 29 mothers of full-term infants, 6 were iron-deficient as evidenced by a low serum iron level with or without anemia. In only one of these was the diet normal, and her infant also had a past history of exchange transfusion for erythroblastosis fetalis with a net loss of hemoglobin (postexchange hemoglobin value of 10.2 gm. %). The serum iron values of an additional four women were also low, but these women were in the late stages of pregnancy, and so the values fell within the range to be expected at that time.[11] Eleven women tested were mothers of premature infants. The serum iron of five of these was low, but three of them were in the late stage of pregnancy. The infants of the remaining two iron-deficient mothers had a history of poor diet. If the two infants of the nonpregnant women are included, four of these five infants had had an abnormal diet.

Twenty-five mothers of nonanemic infants on the wards were studied as controls. Low serum iron values were found in three, two of whom were mildly anemic. There was no significant difference between the serum iron values, iron-binding capacities, hemoglobin concentrations, and hematocrit values of these controls and of the nonpregnant mothers of the iron-deficient infants. Also, there was no significant difference in the per cent of low values between the two groups.

The serum iron and hematocrit values of 23 nulliparous females of good economic background, who were considered "normals," were also measured. The values were similar to those of normal males.

The distribution of serum iron values in anemic infants, their mothers, mothers of nonanemic infants, nulliparous normal females, and normal adult males is seen in Figure 2. The mean values and standard deviations of these groups are tabulated in Table 1.

Thus there is evidence that decreased storage based on low birth weight and, to a less extent, on decreased maternal iron source played some part in the development of anemia in these infants.

The possibility of neonatal blood loss was also investigated by history and, where possible, by hospital record. In one instance such a loss could be documented; it occurred as a result of exchange transfusion for erythroblastosis fetalis, with a

TABLE 1.—*Serum Iron Values*

	Hemoglobin		Hematocrit		Serum Iron		Serum Iron-Binding Capacity	
	Observations, No.	Av. ± S. D., Gm/100 Ml.	Observations, No.	Av. ± S. D., %	Observations, No.	Av. ± S. D., μg. %	Observations, No.	Av. ± S. D., μg. %
Normal males	...	...	...	...	23	130.8±35.2	22	362.2±55.3
Nulliparae	13	13.5±1.1	18	41.2±3.03	22	140.6±31.7	21	394.8±42.1
Control mothers	17	12.4±1.3	22	40.2±3.6	25	114.9±35.9	25	380.3±51.5
Nonpregnant mothers of anemic infants	34	12.2±1.5	31	40.1±3.3	29	96.5±33.1	28	420.1±46.6

net loss of hemoglobin in the process. In a second case there was a history of severe maternal blood loss at delivery, and it is conceivable that this infant may have bled into the placenta.

It was difficult to evaluate the possibility of blood loss during infancy prior to study of the patient. There was no evidence of this by history. Also, when many of these patients were followed without therapy for several months, bleeding was not encountered and there was no drop in hemoglobin values.

To evaluate the part played by dietary habits in the development of iron deficiency in this series, certain standards were established. The criteria for a normal diet were necessarily flexible because of rapidly changing intake during infancy. Milk intake was judged excessive if the infant was under one year of age and took more than 16 oz. over the recommended daily amount or if he was over one year of age and took more than 1½ quarts a day. If he had received no solids by 6 months of age and only minimal solids * without meat or eggs for at least three months preceding the first study, he was considered to have received decreased solids. With use of these criteria, our evaluation of dietary habits attained a certain degree of uniformity.

Fifty-three infants were found to have a history of abnormal diet. Table 2 shows the types and frequency of dietary abnormality encountered. Increased milk combined with decreased solid intake was the commonest finding. A decrease in solids alone was present in a somewhat smaller group. Increased intake of milk without a decrease in solids was relatively infrequent. In addition, there were four cases of malnutrition in which intake of both solids and milk was decreased. Three of these were cases of neglect, while the fourth was a retarded infant with chronic vomiting.

In the remaining 24 cases no dietary abnormality was found. In 13 instances the dietary history was either unavailable or unreliable. Of the remaining 11 patients with well-documented completely normal diet, 4 were premature and may be assumed to have had low neonatal iron stores. The other seven infants were born at full term. The mothers' serum iron was measured in six of these seven and was low in only one case, the patient with a past history of exchange transfusion. The mother of the seventh patient was not anemic, but her serum iron was not measured. Thus, no cause for the anemia could be found in seven cases.

The importance of an abnormal diet in the pathogenesis of severe anemia in younger infants is unknown. There were 11 infants 10 months of age or less. The findings in these infants are summarized

* One serving per day of less than 2 tablespoonfuls of fruits or vegetables was considered to be minimal solids.

TABLE 2.—*Diet of Fifty-Three Iron-Deficient Infants*

Diet	Cases, No.
Normal	11
Unknown or unreliable	13
Abnormal	
(1) Milk increased, solids decreased	30
(2) Milk normal, solids decreased	12
(3) Milk increased, solids normal	7
(4) Milk decreased, solids decreased	4
Total abnormal	53

TABLE 3.—*Summary of Findings in Eleven Iron-Deficient Infants Aged Ten Months or Less*

	Infants							Mothers					
Case No.	Age, Mo.	Birth Weight, Lb., Oz.	Present Weight, Lb., Oz.	Hb., Gm. %	Diet *		Age, Yr.	No. of Pregnancies	Hb., Gm. %	Het., %	Serum Iron, μg. %	Iron Therapy During Pregnancy	Remarks
					Milk	Solids							
1	8	8, 0	.. ..	5.3	N	N	?	4	14.7	44	—	?	Mother taking iron intermittently
2	10	4, 11	18, 13	5.4	D	D	25	5	—	—	—	?	
3	16	6, 8	28, 0	8.5	N	N	27	4	12.4	—	98	Yes	
4	7	5, 9	.. ..	7.0	I	0	?	?	—	—	139	Yes	
5	9	6, 2	13, 10	6.6	N	0	24	5	8.7	28	65	?	Seven months pregnant
6	10	9, 0	20, 8	3.7	I	N	41	7	12.7	41	74	No	
7	8	5+	16, 4	5.9	N	N	32	5	10.6	30	61	?	Six months pregnant
8	10	7, 0	18, 2	4.4	I	D	30	5	11.4	44	56	?	Mother treated for anemia with iron
9	10	6, 14	.. ..	8.0	N	D	28	4	12.5	41	74	Yes	
10	7½	8, 8	20, 8	4.0	I	D	?	?	14.9	45	147	No	
11	6½	6, 9	12, 0	8.5	I	N	37	?	12.4	43	85	No	

* D, decreased; I, increased; N, normal; 0, no intake.

in Table 3. Two of these infants were premature. In one of these infants maternal iron stores were not tested but diet was abnormal. The second premature infant had had a normal diet; maternal serum iron was within normal limits for a late pregnancy. Nine of the infants were full-term, and, of these, seven had taken an abnormal diet. The serum iron of six of the mothers of these latter seven infants was normal while that of the seventh was low. The remaining two full-term infants had taken a normal diet, and neither of their mothers was anemic when studied, although both had been taking iron intermittently.

On classification of the factors contributing to iron deficiency in our patients, the striking findings were the frequency of multiple abnormalities and the very high incidence of dietary deficiency (Table 4). In 54 cases where the information was adequate, 28 were found to have two or more factors contributing to the anemia. In 18 cases, or 33%, only one factor appeared to be responsible. In 14 of these cases the factor was deficient diet; in 3, low birth weight was the single abnormality, and in 1, excessive growth rate was found. In no case was the presence of low maternal iron stores the only abnormality found. Thus, it was dietary deficiency with or without storage deficit that led to iron deficiency in the great majority of these infants.

TABLE 4.—*Relative Importance of Various Factors in the Etiology of Iron-Deficiency Anemia in Infancy*

	Cases, No.
Abnormal diet alone (single factor)	20
Abnormal stores alone	4
Prematurity (single factor)	2
Rapid growth (single factor)	1
Maternal iron/exchange transfusion (double factor)	1
Diet plus stores abnormal (double or more factors)	25
Birth weight/diet	11
Diet/maternal iron	5
Growth/diet	1
Triple factors	9

Comment

While the factors involved in the development of "nutritional" iron deficiency are well known,[10,12] their relative importance in the pathogenesis of this disease has not been clearly demonstrated. Typically, iron deficiency occurs during the period of maximum growth in infancy,[13] at a time when iron stores are at their lowest,[14] and the majority of our cases were detected at this time or soon there-

after. The need for adequate iron stores at birth has been emphasized by many.[15,16] Sixty per cent of iron at birth is present in the circulating blood as hemoglobin, and the liver constitutes the other major reservoir, containing 14% to 22%.[17] The remainder is present throughout the body in myoglobin and enzyme systems.

In premature infants these iron reserves are diminished. The importance of the latter part of pregnancy in the formation of fetal iron stores has long been recognized,[18] and Pommerenke, Hahn, Bale, and Balfour[19] have demonstrated transfer of maternal iron to the fetus in significant quantity as early as the third month of gestation. Vahlquist,[20] in his study of serum iron, demonstrated a steady rise in fetal serum iron during gestation from a value of 20μg. % at the fourth month, perhaps reflecting storage deposition as age increases. However, Iob and Swanson[21] and Widdowson and Spray[22] found that, although the total fetal iron increases as gestation progresses, the concentration per kilogram of water-free and fat-free body substance remains relatively constant. Thus, in the premature infant with his smaller organ size and blood volume, absolute stores are decreased despite adequate relative stores.

In the series of infants reported here prematurity was common. However, it was seldom the single factor present in the development of iron-deficiency anemia and was usually associated with dietary deficiency.

Rarely, if ever, is the infant of an iron-deficient woman born anemic, but tissue iron depletion may be a more frequent complication. Strauss[15] found a significantly high incidence of iron-deficiency anemia in a one-year follow-up of infants of women with iron-deficiency anemia during their pregnancy. Diet and birth weight were said to be normal in these infants, while the maternal anemia was severe in every case. In contrast, Woodruff and Bridgeforth,[23] on analyzing a large series of infants born of women with low hemoglobin values during their pregnancy, concluded that there was no significant difference between the hemoglobin levels of this group and of a suitable control series. However, they stated that although the women in the anemic group had a lower mean corpuscular hemoglobin than the controls few of them could be considered as having definite microcytic hypochromic anemia, indicating a low incidence of true iron-deficiency anemia. It may be that severe maternal depletion is necessary before the fetus is deprived of iron. Our own studies are consistent with this postulate, since none of our iron-deficient women was severely anemic when studied.

Our studies also indicate that maternal iron deficiency only very infrequently leads to iron-deficiency anemia in the infant without the presence of other contributory factors. Since the population of the Boston City Hospital is not representative of the greater Boston area, we compared the mothers of our anemic infants with mothers of nonanemic infants on the wards, presumably of a similar economic and social background. There was no significant difference in the incidence of iron deficiency in the two groups.

Guest and Brown[24] have shown in a large series that there was a significantly lower incidence of iron-deficiency anemia in first-born infants than in later-born infants. However, we could find no difference between number of pregnancies in the mothers of anemic infants and in those of nonanemic infants.

Rarely, neonatal iron depletion may account for diminished storage iron.[15] This may be seen in cases of bleeding from the cord or bleeding into the placenta. It is also an occasional complication of exchange transfusion and was found to be the case in one of the patients of our series. However, such cases are probably unusual.

Allied to the factor of diminished neonatal stores is increased demand for iron in the presence of excessive growth incre-

ment. This was a common but by no means consistent finding among our premature infants. Excessive growth increments were rare in our full-term infants, and the weights of the large majority fell in the lower percentiles. Among those infants who exhibited excessive weight increment, whether premature or full-term, insufficient dietary iron usually occurred simultaneously.

The importance of diet as an etiologic factor in this disease has been debated since the classical findings of Bunge 65 years ago.[25,26] Much of the early work is difficult to evaluate because of technical problems involved in studying iron balance. While Josephs[27] points out that a milk diet supplies a marginal amount of iron and should not lead to the severe anemia which is seen, it is possible that this iron is not in an available form and thus not absorbed in quantities sufficient to prevent severe anemia. Also, as discussed by Sturgeon,[28] physiologic variation in the weights and blood volumes of normal newborn infants may lead to differing iron stores and hence to different dietary needs for iron. Studies of absorption of food iron in both anemic and normal persons indicate that at the most only 10% of food iron is absorbed.[29] Recent studies of infants[30,31] have indicated that there is increased absorption of dietary iron and medicinal iron in normal and iron-deficient infants. However, the quantities absorbed even from a normal diet are just barely enough to provide hemoglobin and nonhemoglobin iron for growth.

Of the factors studied in our series the most frequently found was an abnormal dietary intake. Not only was this a common accessory cause but also it was the only one found with any frequency as the single cause in any given case. The largest number gave a history of decreased intake of solids combined with increased amounts of milk, but a significant number maintained a normal intake of milk in the presence of diminished ingestion of solids. The few patients that ingested a large amount of milk while apparently taking normal quantities of other foods suggest the possibility that milk by virtue of its content of phosphates, or perhaps for some other reason, may occasionally interfere with iron absorption. However, in view of the small number of cases and the many variables in our study, this question must go unanswered. Certainly, the commonest dietary abnormality was that of decreased solids, suggesting that the main problem is lack of available food iron.

It is possible that iron deficiency itself could result in poor appetite with feeding problems and thereby increase dietary difficulties. Perhaps depletion of heme enzymes, as has been demonstrated in animals with iron deficiency,[32,33] may play a part.

The increased incidence of males and Negroes in the cases studied seems in both instances to be related to dietary habits. There was no preponderance of prematurity among the males; rather, the reverse was true. Also, there was neither any greater growth rate nor a greater incidence of iron-deficient mothers of male anemic infants. Abnormal diet was the main etiologic factor in this group, as it was in the total iron-deficient population. Also, in the Negroes of our series there appeared to be a high familial incidence of iron-deficiency anemia presumably secondary to abnormal diet. When studied, maternal iron stores were normal in such cases. In the Negroes there was a slightly higher incidence of lower birth weights, but analysis of the cases revealed again that abnormal diet was the commonest factor. The figures suggest that there is a greater incidence of abnormal dietary habits among our hospital population of Negroes and males.

Hoag, Wallerstein, and Pollycove[34] have emphasized the importance of chronic blood loss in causing iron-deficiency anemia in infancy. Although we found no evidence of this factor being a major one in our series, the seven infants with no known

cause for the anemia may have suffered undetected blood loss, as may also have been the case in our nine young infants whose maternal iron stores were normal. Since we could not be certain of occult blood loss, we have recently undertaken to test all stools of our iron-deficient infants for blood loss, and of 23 patients only 4 were found to have positive tests for occult blood, none of them persistent. In the type of population reported here, then, blood loss does not seem to play a major part in the development of iron-deficiency anemia.

Summary

Of the factors investigated the most frequently found was an abnormal diet. In those cases in which only one cause was found the large majority were due to abnormal diet. Low birth weight was much less frequently the single factor, and low maternal iron stores never acted alone, although in a larger series the latter factor might have been implicated as operating singly. Abnormal weight increment in full-term infants was also only rarely encountered as a cause of iron-deficiency anemia. It appears, therefore, that, given a normal diet, an infant overcomes his relative neonatal iron deficit. However, normal iron stores at birth are not adequate to prevent the development of iron-deficiency anemia in the presence of an abnormal diet.

Dr. Eve Wiltshaw assisted in a portion of this study, and many members of the pediatric service of the Boston City Hospital allowed us to study their patients.

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Clinical Study of Oral Phenoxymethyl Penicillin and Parenteral Procaine Penicillin G

Comparative Study of Results in 1266 Children

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The recent introduction to clinical medicine of phenoxymethyl penicillin (penicillin V) has for the first time provided a penicillin which is virtually insoluble and therefore stable in the pH range of gastric juice. In the alkaline media of the intestines this preparation is soluble and therefore readily absorbed.

Reports indicate that orally administered phenoxymethyl penicillin produces blood concentrations considerably higher than a comparable dose of penicillin G. Following oral administration of phenoxymethyl twice as much penicillin is excreted in the urine in an active form as following oral administration of penicillin G. The activity of phenoxymethyl penicillin is similar to that of penicillin G. However, penicillin blood levels attained with the orally administered phenoxymethyl penicillin preparation are lower and less uniform than blood levels from equal doses of crystalline penicillin G given parenterally.[3]

The blood levels attained with orally administered phenoxymethyl penicillin are superior to levels obtained from comparable doses of intramuscular procaine penicillin G.[4]

The desirability of avoiding injection therapy in children both from the emotional and technical point of view encouraged us to carry out a comparative clinical evaluation of orally administered phenoxymethyl penicillin and parenterally administered procaine penicillin G.

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From the Department of Pediatrics, Baylor University College of Medicine, and the Pediatric Service of the Jefferson Davis Hospital.

Plan of the Study

The study group included 2132 children who were admitted to the pediatric clinic with the usual acute infectious diseases seen in a large outpatient department serving an indigent population.

Each patient was seen by a physician, and, after careful clinical evaluation, therapy was prescribed. While the decision to administer a penicillin preparation was the prerogative of the examining physician, he was not aware of the particular regimen to be followed. Alternate patients were treated with either Regimen 1 or 2, as follows.

Regimen 1. Procaine penicillin G; children under one year of age were given 300,000 units daily, while children over one year of age were given 600,000 units daily, for a period of five days.

Regimen 2. Phenoxymethyl penicillin, 125 mg. (200,000 units) orally every six hours for five days. Cultures of the involved area and white blood cell counts were obtained on every fifth patient. All patients were instructed to return on the last day of therapy for evaluation of their response. Special attention was given to acceptability and tolerance. The response of the patient to treatment was evaluated at the time of following up as follows: A indicated no disease; B, improved; C, not improved; D, hospitalized.

In patients in whom β-hemolytic Streptococci were isolated, penicillin therapy was continued for 10 days, as per recommendation of the American Heart Association.

Results

Table 1 summarizes the over-all results of the study. Of the 2132 patients treated, 1266, or 59%, returned on the last day of therapy for evaluation. Since all children treated in this clinic are medically indigent, and this is the only clinic in the area serving this clientele, it is probable that all who

TABLE 1.—*Summary of the Therapeutic Results in all Patients Studied*

Status Following Penicillin Therapy	Patients, No.	
	Phenoxymethyl Penicillin by Mouth	Intramuscularly Procaine Penicillin G
No disease or improved	1,032	1,023
Not improved or hospitalized	34	43
Totals	1,066	1,066

TABLE 2.—*Comparative Study of Phenoxymethyl Penicillin by Mouth and Procaine Penicillin G Intramuscularly*

Type of Therapy	Status Following Penicillin Therapy			
	A No Disease	B Improved	C Not Improved	D Hospitalized
Parenteral				
Procaine penicillin G only	238	18	14	7
Procaine penicillin G plus other therapy *	311	32	14	8
Total	549	50	28	15
Oral				
Phenoxymethyl penicillin	221	17	7	8
Phenoxymethyl penicillin plus other therapy *	320	32	11	8
Total	541	49	18	16

* Sulfonamides, tetracycline, or chloramphenicol.

did not return were either cured or sufficiently improved to carry on without further medical care. The number of patients failing to return on the fifth day was similar in the two therapy groups.

Table 2 summarizes the total number of patients who returned for follow-up evaluation on the fifth day and the result of their therapy.

TABLE 3.—*Initial Clinical Diagnosis in 1266 Patients Who Returned for Evaluation After Five Days of Penicillin Therapy*

Diagnosis	Phenoxymethyl Penicillin Orally								Procaine Penicillin G Parenterally							
	No Other Drugs				With Other Drugs				No Other Drugs				With Other Drugs			
	A *	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Otitis media	28	4			53	7	2		35	3	3		50	5	4	
Tonsillitis	60	3	1	1	43	5	3		81	5	4	2	57	2	3	
Upper resp. inf.	70	7	2	4	106	6	3	4	59	3	5	1	89	11	5	2
Pneumonia	24	2	1	1	66	7		2	25	1		2	35	6		3
Bronchitis	8			2	8	1			13	1	1		6			
Pyoderma	6	1		1	10	4			13	1	1		4	5		
Cellulitis	12		1		11				7				11			
Adenitis	2				3	1			1			1	1	2	1	
Misc. acute illness	8	0	3		10	1	3	0	13	2	1	2	5	1	1	6

* A, B, C, and D indicate status as shown in headings of Table 2.

In order to demonstrate the similarity of the two groups, Tables 3 through 6 present the diagnosis, culture results, and blood cell counts of the series. As can be seen, the groups are similar in every respect, not only when penicillin in either form was used alone but also in the groups treated with multiple antimicrobial agents.

Initial bacteriologic studies were obtained in 204 children. Of this group repeat cultures on the fifth day were studied in 109 cases (Table 5), with the following results.

1. No pneumococci were present on repeat culture regardless of the type of penicillin used.

2. β-Hemolytic streptococci were still present in 30% of the patients on the fifth day, regardless of therapy, but after 10 days of therapy they were not present.

3. In patients who had repeat cultures, as many or more Staphylococcus pyogenes var. aureus organisms were present after therapy than before, regardless of type of penicillin used or whether it was used in

TABLE 4.—*Bacterial Organism Isolated from the Involved Area Prior to Therapy*

Organism Cultured	Phenoxymethyl Penicillin Orally				Penicillin G Injection			
	A	B	C	D	A	B	C	D
α-Streptococcus	53	8	4	1	44	6	3	
β-Streptococcus	28	4	1		28	3	1	
Pneumococci	10				5		2	
Neisseria	28	5			16	4	2	
Staph. pyogenes var. albus	21	1	1		17	4		
Staph. pyogenes var. aureus	34	8	4	2	23	3	3	
E. coli	9	2			9	1		1
Proteus	2	1					1	1
Klebsiella					4			
Pseudomonas	2	1			3			

TABLE 5.—*Post-Treatment Bacteriology for β-Streptococcus, Pneumococci, and Staphylococcus Pyogenes Var. Aureus*

Organism Cultured	Phenoxymethyl Penicillin Orally				Procaine Penicillin G Parenterally			
	No Other Drugs		With Other Drugs		No Other Drugs		With Other Drugs	
	Before	After	Before	After	Before	After	Before	After
β-Streptococcus	14	2	19	3	18	11	13	7
Pneumococci	2		4		3		4	
Staph. pyogenes var. aureus	11	10	13	14	10	11	9	9

combination with a sulfonamide drug or tetracycline medications.

Tables 7 and 8 summarize the reactions and acceptance of the groups given penicillin without other drugs. It can be seen that the favorable acceptance of the orally administered preparation probably justifies the slightly higher incidence of reactions, which did not appear statistically significant. When the orally administered preparation was discontinued, the skin manifestations cleared in 24 hours in all four patients. This also occurred in the two patients treated with penicillin intramuscularly.

In the groups showing no improvement in the five-day period or those requiring hospitalization, the final outcome actually revealed fewer failures than is initially indicated in Table 3. Numerous children were found to have viral diseases or to require surgery for inflammatory masses or were admitted for fluid therapy only; their conditions were, therefore, necessarily not within the realm of penicillin-treatable diseases. Table 9 shows these failures by diagnosis.

TABLE 6.—*The White Blood Cell Count in 323 Patients Selected at Random from the Study Group*

Clinical Status	Oral Group			Injection Group		
	Normal WBC	Elevated WBC	Total	Normal WBC	Elevated WBC	Total
A	34	98	131	33	106	139
B	8	7	15	6	6	12
C	4	1	5	1	2	3
D	1	7	8	1	9	10
Total counts			159			184

TABLE 7.—*Reactions Observed in the Course of Observation of 530 Patients Receiving Either Oral or Parenteral Penicillin Therapy Alone*

Reaction	Therapeutic Agent	
	Phenoxymethyl Penicillin Orally	Procaine Penicillin G Parenterally
Skin rash	4	2
Vomiting	1	0
Total treated	253	277
Per cent of total showing some reaction	2.0	0.8

Chemistry

The understanding of penicillin and its many forms necessitates an examination of its structural formula.[5]

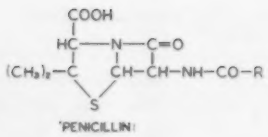
The basic structure is the same regardless of the form, the differences being found in the "R" fraction.

R	Radical	Designation
$-CH_2(CH_2)_2CH_3$	*n*-amyl	dihydro F
$-CH_2(CH_2)_5CH_3$	*n*-heptyl	K
$-CH_2C_6H_5$	benzyl	G
$-CH_2OC_6H_5$	phenoxymethyl	V

The addition of various precursors to the synthetic media in penicillin biosynthesis will make possible the formation of various forms, all of which have the same basic

TABLE 8.—*Acceptability of Therapeutic Agent to Child*

Acceptability	Therapeutic Agent	
	Phenoxymethyl Penicillin Orally	Procaine Penicillin G Parenterally
Good	226	0
Fair	20	277
Poor	7	



'PENICILLIN'

microbiologic activity but which differ in their absorption, blood levels, and excretion. By the further addition of substances such as procaine or benzathine one may further modify the serum levels, regardless of the original penicillin salt utilized.

Phenoxymethyl penicillin has the unique advantage of being insoluble in the acid pH of the stomach but soluble and readily absorbed in the alkaline media of the small intestines. This preparation is a product of biosynthesis and is intended for oral use.

Pharmacology

Mice and rats tolerated phenoxymethyl penicillin by all routes of administration at doses in excess of 3,200,000 units per kilogram. This form is not more toxic than procaine penicillin, in fact, when given intravenously, it was found to be 8 to 10 times less toxic.[5]

Blood levels on comparable doses of phenoxymethyl penicillin and penicillin G when given orally have been published and reveal a significant advantage in favor of the phenoxymethyl form. The results given in Table 10, by Wright and co-workers,[6] demonstrate these levels.

Summary

A comparative clinical study of phenoxymethyl penicillin (penicillin V) given orally and parenterally administered procaine penicillin G was undertaken in 2132 children, with the following results.

TABLE 9.—*Type of Medication and Clinical Diagnosis in Patients Who Were Unimproved at the End of Five Days of Penicillin Therapy*

Diagnosis	Phenoxymethyl Penicillin Orally				Procaine Penicillin G Parenterally			
	No Other Drugs		With Other Drugs		No Other Drugs		With Other Drugs	
	C	D	C	D	C	D	C	D
Upper respiratory infection	2		1	2	6		5	
Tonsillitis			2		3		1	
Otitis			4		3		4	
Bronchitis		2			1			
Herpetic Stomatitis					1			
Cellulitis	2			1			1	
Rubella							2	
Parotitis							1	
Rubeola	1							
Pneumonia	1	2		2		2		2
Cat-scratch fever			1					
Infectious mononucleosis	1		1					
Nonspecific vaginitis			1					
Enteritis			1					2
Peritonsillar abscess						1		
Adenitis						1		
Primary tuberculosis						1		
Meningitis						1		2
Rheumatic fever								2
Staphylococcus sepsis		1		1				
Nephritis		2						
Paroxysmal tachycardia		1						
Bone cyst				1				

Of the total group, 1266 patients (59%) returned for follow-up.

Of children with infections seen in our clinic, initial cultures revealed only 40% with an organism which might be influenced by penicillin.

When penicillin was administered, nearly all of these children were well within five days.

Those patients harboring β-hemolytic streptococci achieved negative cultures in

TABLE 10.—*Blood Levels of Phenoxymethyl Penicillin and Penicillin G*

	Cases, No.	Blood Level, Units/Cc.			
		1 Hr.	2 Hr.	4 Hr.	6 Hr.
Phenoxymethyl penicillin	50	1.044	0.438	0.128	0.029
Penicillin G	48	0.699	0.201	0.061	0.013

about the same period, regardless of the method of administration of penicillin.

There were no significant differences in the number of side-reactions in the two groups.

Dr. C. W. Daeschner gave guidance in the study.

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Analysis of Protein Skin Reactivity in Infantile and Childhood Eczema

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In a previous paper[1] we discussed the dermal-respiratory aspect of allergy in a series of allergic infants and children. We are here concerned chiefly with an appraisal of the skin tests in these cases. The cases to be described consist of 114 infants and children all of whom had eczema when they were first seen. These include 42 infants (under 2 years) with eczema alone, 38 children with eczema alone, and 34 infants and children with eczema and a complicating respiratory allergy.

Other publications in the literature have reported on skin test findings. We believe that our study is unique in the sense that each case was tested with at least 350 different proteins. Further, where it was difficult to interpret results, tests were repeated.

For the most part the tests were performed by the scratch method. Early in the study the intradermal method was not employed in all cases. Subsequently, intradermal tests with inhalants and pollens were included in all. We learned that intradermal tests to inhalants and pollens in the young children are essential, because young children usually have a low grade of sensitivity to these substances and the scratch test does not reveal their presence as often as does the intradermal test. Scratch tests with foods, on the other hand, are quite satisfactory, intradermal tests giving too many false-positive results.

About 97% reacted to one or more skin tests, which are described in Table 1.

TABLE 1.—*Summary of Types and Groups of Positive Skin Reactivity to Protein*

Materials Eliciting Positive Reactions	Infants with Eczema Alone, %	Children with Eczema Alone, %	Ratio of Infants to Children
Total reactors	97.5	97	1:1
Total foods	96	81	1.2:1
Total inhalants	62	74	0.8:1
Total pollens	24	50	1:2
Foods alone	31	13	2.4:1
Inhalants alone	2.5	8	1:3
Pollens alone	0	3	0:3
Foods & inhalants	40	26	1.5:1
Foods & pollens	5	8	1:1.6
Inhalants & pollens	0	5	0:5
Foods, inhalants & pollens	19	34	1:1.8

Viewed from an over-all standpoint, many striking features are found. For example, rarely, if ever, does one find pollen reactions alone in eczema, whereas a fair percentage of persons with eczema react to foods alone, and this finding is commoner in infants. Total food reactors are found in the largest number of eczema cases, but

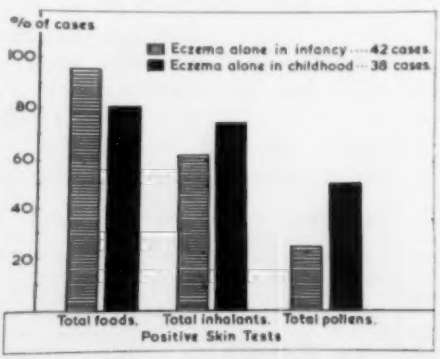

Chart 1.—Comparison of positive skin tests in eczema of infants and children.

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† Dr. Ratner died Oct. 11, 1957.

TABLE 2.—*Comparison of Tests in Uncomplicated Eczema and Dermal-Respiratory Syndrome*

Materials Eliciting Positive Reactions	Eczema Alone, %	Dermal-Respiratory Syndrome, %	Ratio of Eczema Alone to D-R Syndrome
Total foods	89	80	1:1
Total inhalants	68	91	1:1.3
Total pollens	34	82	1:2.4

the reactors to inhalants are a close second, the former being commoner among infants and the latter, commoner among children (Table 1 and Chart 1). It was surprising for us to find 24% of infants reacting to pollens in combination with other substances (Table 1). That twice as many children reacted to pollens was what one would expect. The largest number that reacted to a single group of allergens alone reacted to foods. Insignificant numbers reacted to inhalants alone, pollens alone, or even inhalants and pollens combined. We must thus conclude that the majority of patients with eczema presented in this series reacted to foods alone or in combination with inhalants and pollens.

It was interesting to note that almost twice as many infants as children reacted to the combination of foods and inhalants, whereas almost twice as many children reacted to the combination of foods, inhalants, and pollens.

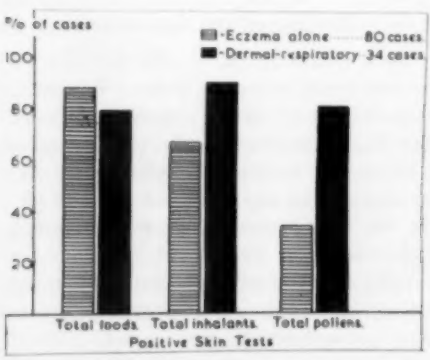

Chart 2.—Comparison of positive skin tests in pure eczema and dermal-respiratory syndrome.

We discovered that repetition of tests after a year was essential if the eczema did not clear. As the infant grew older and inhalant and pollen sensitivities were revealed, prophylactic measures and early treatment of these sensitivities could be instituted.

Analysis of Table 2 and Chart 2 (pure eczema cases in relation to the dermal-respiratory group) discloses a trend similar to that noted in Chart 1. The total food reactors are about evenly distributed between the pure eczema and the dermal-respiratory group, with a slight preponderance among the cases of pure eczema. Inhalant sensitivities are also found in a large percentage of cases. There are relatively few pollen reactors in the pure eczema group, comprising but 34% of the cases. Here we find the most significant difference between the two groups, because 82% of the dermal-respiratory group are sensitive to pollens.

TABLE 3.—*Relative Order of Frequency of Positive Reactions to Protein Skin Tests in Eczema in Infants and Children*

	Infants		Children	
Order of Frequency	Antigenic Test Material	Per Cent Positive	Antigenic Test Material	Per Cent Positive
1st	Egg	64	Vegetables	63
2d	Vegetables	60	Inhalants	61
3d	Inhalants	52	Fish	48
4th	Fish	50	Fruits	42
5th	Fruits	50	Condiments	42
6th	Meats	40	Egg	37
7th	Nuts	38	Nuts	37
8th	Wheat	33	Bacteria	35
9th	Condiments	29	Cereals	26
10th	Milk	26	Wheat	24
11th	Cereals	19	Meats	24
12th	Pollens	19	Pollens	24
13th	Bacteria	18	Milk	16
14th	Molds	12	Molds	8
15th	Chocolate	10	Chocolate	8

Table 3 shows the order of frequency of the positive scratch tests and gives the per-

TABLE 4.—*Review of the Literature on Positive Skin Tests in Eczema*

Author	Cases, No.	Age Range	Other Allergies	Method of Testing	Per Cent Positive Reactions with								
					Whole Egg	Egg White	Wheat	Whole Milk	Lactalbumin	Cocoa	Food	Inhalants	Pollens
Ramirez [5]	78	Children & adults				18	2.5	5					
Herman [3]	30	5 wk. to 7 yr.			40		20	13					
Piness & Miller [4]	293	Children & adults	Asthma or hay fever in 81%	Scratch & i. c.*	18		15	9		4	80	32	52
O'Keefe & Rackemann [8]	239	Children	Asthma in 11%	Scratch	39		15	14					
Peck & Salomon [6]	50	Children	Some had respiratory allergy			32	12		4				
Hill [7]	300	Infants & children			44		12	15					
Hill [9]	127	Children		Scratch	40		12	8					
Hill & Sulzberger [9]	29	Under 3 mo.			56			24					
	46	6 mo. or under				91 †	15 †	24 †					
	46	6 mo. to 1 yr.				85 †	28 †	28 †					
	46	2-12 yr.				61	13	13					
Hill [11]	100	Under 1 yr.		Scratch		86	17	26					
Netherton [12]	50	Children & adults	Present in 27		52		44	48				98	
Farmer [14]	50	Infants & children	Asthma in 32	Scratch		60	17	14				Prominent	Prominent
Ross & Brown [18]	85	Infants & children		i. c.	25		24	17		6			

* Intracutaneous injection.
† Includes positive reactions only.

centage of positive reactions in each group.*

Many interesting general observations can be made from this Table. The first is the high incidence of positive reactions to egg in infants, with a fall to almost one-half in childhood. The high incidence of positive reactions to vegetables is surprising. However, it should be noted that this particular incidence is weighted by the fact that each subject was tested with 20 to 30 vegetables. The relatively low incidence of reactions to wheat is also noteworthy. It is rather interesting that chocolate, which has always been heralded as a frequent offender in eczema, is found to fall into the lowest order of frequency for both infants and children. That inhalants assume third place in infancy and second place with older children is significant. The fact that milk assumes 10th place in infancy and 13th in older childhood may perhaps be attributed to more careful infant feeding today, with the use of evaporated milk and other denatured foods. The higher order of frequency of condiments in older children than in infancy is undoubtedly due to greater consumption in the older age group. The higher order of bacterial reactions in children is related not alone to the chronicity of eczema, with superimposition of secondary infection, but also undoubtedly to the element of exposure.

* It will be noted that the total reactions for inhalants and pollens are lower in Table 3 than they are in Table 1 and Chart 1. This is because intracutaneous tests with inhalants and pollens as well as scratch tests are included in Table 1 and Chart 1, whereas Table 3 considers only those tests done by the scratch method.

Review of the Literature

In a consideration of the literature on protein sensitization in eczema it must be remembered that we are dealing with sensitivities determined by scratch testing, intracutaneous testing, elimination diets, or a combination of any two or all of these (Table 4). The general trend of these findings agrees with our results.

Hill and Sulzberger [9] stated that egg, wheat, and milk are the most important food atopens in infantile eczema.

In another paper [10] (1935) Hill discusses environmental allergens in infantile eczema.

In 100 cases of eczema he found that 10% under 1 year of age, 24% from 1 to 2 years, and 50% from 2 to 12 years reacted to inhalants and/or pollens. We also found this increased percentage with advancing age.

Sulzberger and Wolf [13] (1940) expressed the opinion that cow's milk, wheat or other cereals, and eggs are the most important dietary allergens in infantile eczema.

Urbach [15] (1943) states that among a group of patients, mostly children but also adults, with atopic dermatitis in whom the principal cause of the dermatitis was hypersensitiveness to foods, the most commonly encountered allergens were egg, milk, flour, fish, and meat. He also states that the majority of all children with infantile dermatitis give a positive reaction to raw egg white.

Feinberg [16] (1946) states that egg, wheat, and milk are frequently at fault in atopic dermatitis.

Hill [17] (1947) again points out that egg white is the commonest allergen to which infants with atopic dermatitis are sensitive but that fish and nuts are not uncommon.

Comment

Protein skin testing is diagnostically the bedrock of clinical allergy. History analysis is perhaps in many respects of equal importance; nevertheless, without skin tests the exact diagnosis and treatment of allergy would not, in our estimation, have made the strides it has.

Since the reactions detailed here are biological and the interpretation of skin tests at times somewhat subjective, it may be contended that our data are not entirely objective and hence scientifically subject to question. However, certain trends and observations can be gleaned from these data which are consonant with those of other observers and should help in a better understanding of the eczema problem.

That food reactions occur in the largest number of eczema cases in infants and children is not at all unexpected, but that inhalant sensitivities should also show so high an incidence is a finding which places a totally different complexion on the problem of eczema. The prominent role which combinations of foods and inhalants and/or pollens play in eczema brings further evidence to bear on the importance of the concept which we voiced in a previous publication on the dermal-respiratory syndrome.[1] This observation of the dual nature of the sensitivity in eczema makes it evident that it is not a dermal disturbance alone but that there exists in conjunction a respiratory component. In 59% of all eczema cases, if our experience is borne out further, one must be prepared for the contingency of the subsequent development of asthma, hay fever, or allergic rhinitis.

Several facets of food sensitivity are worthy of discussion. In the first place, the total food reactors were about evenly distributed between the pure eczema and the dermal-respiratory group, with a slight preponderance among the cases of pure eczema.

The order of frequency of positive tests presents material of practical and interpretive value.

First, we might note the high incidence of egg sensitivity in infancy, with a fall to almost one-half in later childhood. Ratner and Untracht [19] reviewed this question and attributed the extraordinary finding to sensitization of infants in utero as a result of the consumption of egg white in relatively large amounts by the pregnant woman, its easy diffusibility through membranes, and its resistance to digestive enzymes. Egg sensitivity cannot be judged solely from a study of skin sensitivity, for positive skin reactions to egg outnumber those with clinical significance. The final interpretation of egg skin sensitivity (as well as other food sensitivities) must rest on careful appraisal of whether the reaction is due to a waning previous sensitivity which is no longer of clinical significance or whether the dermal reaction is indicative of

an existing clinical sensitivity. Previously we reported that, although 10% of our cases reacted to egg white, only 4.5% were clinically sensitive.[19] These observations are of value in the interpretation of food sensitivity in general and the interpretation of skin reactivity in particular. Residual skin sensitivity may be present long after clinical tolerance has been established.

The relatively low incidence (8th and 10th in order) of wheat sensitivity is also noteworthy. This, we believe, is largely due to the consumption of cooked cereals, which have been shown by us[20] to be reduced in allergenicity through the process of cooking.

That chocolate falls into the lowest order of frequency has been long known to us, and its low order of sensitivity has been observed by others. This, we believe, is due to its consumption in cooked form. Why this particular food has been the one food that most physicians eliminate in cases of eczema we do not know. It is obvious from our findings and those of others that this food is not an important factor in eczema.

The fact that milk has dropped to 10th place in infancy and 13th in older children, when in the past it was among the first three allergens, merits some remarks. It is a fact that milk was in the upper bracket of substances causing sensitivities in infants and children years ago, and the literature was replete with evidence of its frequency and severity. Since it was recognized through the studies of Lewis and Hayden[21] and Ratner and Gruehl[22] that a reduced allergenicity was found in boiled and evaporated milks, as compared with raw milks, these milks became more popularly used for infant feeding. At present the overwhelming majority of infants are fed evaporated milks, and it is our conviction that their use has led to this precipitous fall in milk sensitivity. Recently a survey was made[23] on milk sensitivity by questioning a large group of pediatricians and allergists, and the low incidence of 1.5% was found.

Were we to return to feeding raw cow's milk, we believe there is little doubt that the incidence of milk sensitivity would rise again to its former high point of eminence. The principle of the heat denaturation of foods in the management of allergic patients should not only be applied to milk but should be carried over to vegetables and other foods.[24] We are great consumers of raw vegetables, and that, we believe, accounts for the high position of the scale that vegetables hold at the present time.

That inhalants assume third place in infancy and second place in older children is a truly significant observation and obviously presents a challenge for greater efforts to reduce contact with these substances. The fact that both pollens and inhalants enter the picture in analysis of eczema cases has been evaluated in our preceding paper[1] and considered above.

The higher order of frequency of condiments and of bacterial reactions in older children than in infancy, we believe, is related in the former instance to greater consumption and in the latter instance to the chronicity of eczema, with the superimposition of secondary infections, and to the increased exposure to bacteria by other routes.

The further analysis of the food sensitivities in those who react to foods alone shows that it is rare for a patient to react to a single food or food alone. When food sensitivity is under consideration the factor of multiple reactions should be borne in mind. It is evident, then, that if an infant is sensitive to milk and is given one or another form of milk substitute and a good result is not obtained the allergic reaction may be due to some other sensitivity to food and/or inhalant.

Summary and Conclusions

A high incidence of positive skin reactions was found in infants and children with eczema.

The final interpretation of food sensitivity must rest on clinical corroboration for a residual skin reaction, for food sensitivity may remain for years after clinical tolerance has been established.

Although foods play an important role, few patients react to foods alone, but rather they react to foods in combination with inhalants and/or pollens.

Compared from the standpoint of age, reactions to foods and inhalants were found in twice as many infants as children, whereas twice as many children reacted to combinations of foods, inhalants, and pollens.

The intradermal test with inhalants and pollens is essential in young children, because they usually have low-grade sensitivities to these substances and the scratch test often does not reveal their presence.

One must view the problem of eczema as a complex allergic phenomenon, and due consideration must at all times be given to sensitizations encompassing the several groups of allergens, foods, miscellaneous inhalants, pollens, molds, and bacteria.

The order of frequency of reactivity in infants was egg, vegetables, inhalants, fish, fruits, meat, nuts, wheat, condiments, milk, cereal grains, pollens, bacteria, molds, and chocolate.

The order of frequency in children was vegetables, inhalants, fish, fruits, condiments, egg, nuts, bacteria, cereal grains, wheat, meats, pollens, milk, molds, and chocolate.

The high incidence of inhalants suggests that the dermal manifestations are forerunners of the future sequels of asthma and of hay fever.

The low order of frequency of milk allergy, we believe, is attributable to the widespread use of heat-treated milks, such as evaporated milks and low-sodium milk (Similac), in infant feeding.

It is rare that an infant reacts to one food alone, and the majority react to multiple foods as well as inhalants and/or pollens.

If skin tests are to be of value, a large number should be employed in order to ferret out as many factors as possible that are involved in the patient's allergy.

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Case Reports

Salt-Losing Nephritis

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Salt-losing nephritis is one of many clinical situations involving electrolyte disturbance in renal disease. This type of nephropathy is characterized by hyponatremia and hypochloremia, lassitude, thirst, polyuria, azotemia, and circulatory collapse. The syndrome was first described by Thorn, Koepf, and Clinton [1] in 1944. Since then, 15 additional cases have been reported [2-11] which satisfy the criteria of Levere and Wesson [9] for salt-losing nephropathies.

The purpose of this report is to present the first case of salt-losing nephritis in the pediatric age group and to outline the therapeutic regimen based on the pathophysiology of the syndrome.

Report of Case

A 12-year-old white boy was admitted to Montefiore Hospital on Aug. 10, 1956, for the third time because of expectoration of bloody material. The first two admissions were on the private service on April 7, 1956, and July 11, 1956, for anemia.

He was transfused on each admission but received no other diagnostic study than a determination of blood urea nitrogen. This was discovered to be 153 mg. % on July 11, 1956. His blood pressure then was 130/90 mm. Hg. The significance of these findings was explained to the parents. Despite this, they refused to allow further investigation and demanded the child's discharge on July 13, 1956.

The neonatal history was normal. At about one year of age the patient exhibited an intermittent fever (temperature from 101 to 103 F), which was attributed to "teething." At the same time polyuria and polydipsia were noted. The duration of this episode was measured in months and was known to have subsided spontaneously at the age of 2 years. He was then well until he was 9 years old, when he against presented polyuria and polydipsia with a craving for salt. At the age of 10 he presented one episode of carpopedal spasm and cramps in the legs which was suggestive of tetany. He was treated by his family physician. The nature of the therapy was unknown, and no recurrences were noted.

Eighteen months prior to this hospitalization the child was admitted to another hospital for investigation of his excessive thirst. At that time the significant findings were blood pressure which varied between 110/80 and 140/80, mild anemia, and elevated blood NPN of 50 mg. %. Other studies included a "Pitressin test," which showed little variation in urine flows, the rate of flow measuring 2.4 cc. per minute before the injection of 5 milliunits of vasopressin (Pitressin) intravenously and 2.1 cc. per minute for three hours after the injection. A water-deprivation test was performed in which the intake was limited to 1000 cc. in 30 hours. The urinary output during this period of time was 3000 cc., with a specific gravity of 1.010, and the blood NPN rose to 78 mg. %. No amino-aciduria was discovered, and there were no formed elements in the urine. The urine "showed a great loss of both sodium and chlorides above normal values" and an occasional positive test for albumin. Retrograde pyelogram and cystoscopy were normal. The child was discharged with a diagnosis of nephrogenic diabetes insipidus secondary to renal disease of undetermined etiology.

Following discharge, the child remained listless and continued to crave salt and water in such quantities that the parents attempted to restrict them.

The present admission, in August, 1956, was for nausea and vomiting of a dark-colored material. The child was more listless than usual and complained of muscle cramps.

Physical examination revealed a lethargic, tachypneic, moderately well-nourished, but chronically ill child. His height was 132 cm., and his weight was 26 kg. Blood pressure was 150/95; pulse rate was 108; respiration rate was 44; temperature was 99 F. A papular, lichenified skin

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From the Pediatric Service of Montefiore Hospital.

TABLE 1.—*Blood Chemistry Values of the Patient*

Date	Bun, Mg. %	Creatinine Mg. %	CO_2, mEq/L.	Cl, mEq/L.	Na, mEq/L.	K, mEq/L.	Ca, Mg. %	P, Mg. %	Alkaline Phosphatase, Bodansky Units
8/11	199	11.5	8.6	79.6	116	5.7	--	--	--
8/13	195	11.5	8.4	78.0	121	5.8	5.9	15.0	4.0
8/14	--	--	--	--	--	--	6.1	13.7	6.9
8/15	--	--	--	--	114	6.3	--	--	--
8/17	200	12.3	10.4	72.0	118	6.1	6.8	13.1	--
8/20	130	10.6	10.9	89.0	121	3.0	6.6	5.2	--
8/23	133	--	14.0	95.0	127	4.3	8.0	7.2	--
8/27	153	--	12.2	94.8	131	4.3	--	--	--
8/29	138	9.2	16.3	96.4	130	4.1	8.4	4.2	--
8/31	111	9.3	18.6	99.0	137	4.6	--	--	--
*9/10	71	9.0	19.0	108.0	141	6.0	9.0	6.0	--
10/24	55	10.0	19.0	100.0	142	6.0	11.0	4.0	--
11/20	--	--	17.0	100.0	138	6.0	--	--	--
12/12	101	13.0	13.0	101.0	132	5.0	8.0	8.0	--

* Values obtained during clinic visits.

rash was present over the torso. Funduscopic examination was negative. The right buccal mucosa was excoriated and bleeding. The gingivae were reddened and bleeding, but no vesicles were noted. Lungs, heart, and abdomen were within normal limits. Neurological examination revealed a somewhat cloudy sensorium. A positive Chvostek sign was elicited, and fasciculations in the calf muscles were present. The Trousseau sign was negative.

Urinalysis on numerous occasions showed a specific gravity between 1.004 and 1.010, with a weakly acid reaction, the pH varying from 5.5 to 8; albumin was present from 1+ to 3+; no hematuria, pyuria, or cylinduria was ever noted. Hemoglobin on admission was 7 gm.; RBC 3,200,000; hematocrit, 25%; WBC, 9000, with a normal differential count. Fasting blood sugar was 84 mg. %. Total protein was 7.2 gm., with an al-

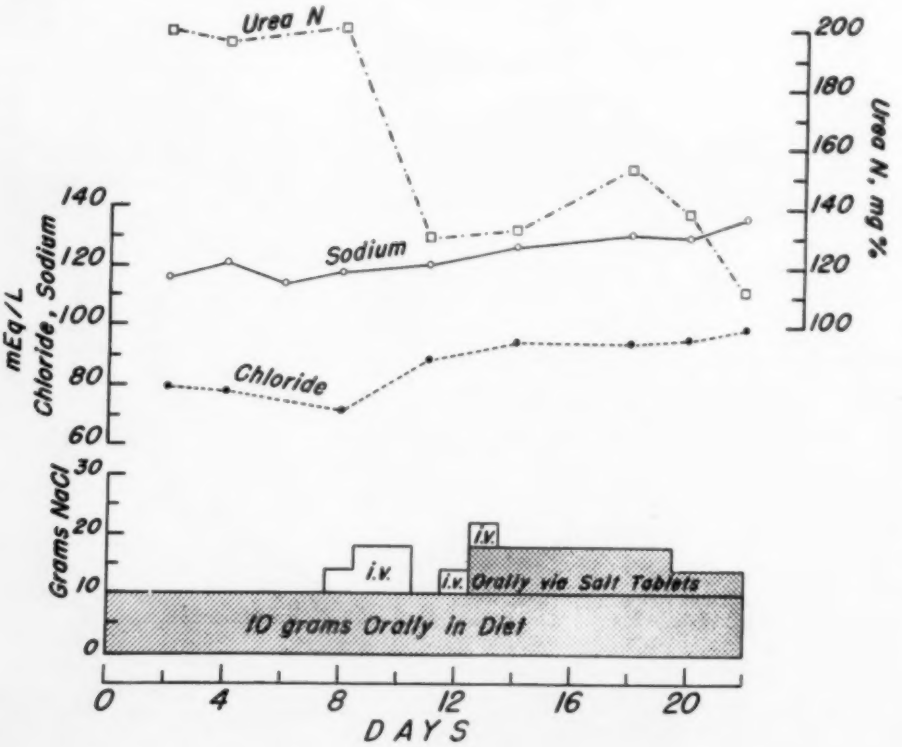

Figure 1

TABLE 2.—*Urinary Electrolytes*

		Sodium		Chloride		Potassium		Ammonia		
24 Hr. Period	Vol., Ml.	mEq/L.	mEq/24 Hr.	mEq/L.	mEq/24 Hr.	mEq/L.	mEq/24 Hr.	Mg. %	Mg/24 Hr.	pH
8/12-8/13	1340	58.0	78.8	46.0	62.1	21.0	28.2	--	--	--
8/13-8/14	997	48.0		46.5		21.0		--	--	--
8/16-8/17	650	49.0	29.5	35.6	21.4	20.0	35.6	--	--	--
8/17-8/18	595	39.8	23.7	33.6	20.0	18.5	11.0	--	--	--
8/19-8/20	5100	76.0	388.0	65.0	332.0	18.0	92.0	84.8	432.0	--
8/20-8/21	1140	72.0	82.2	68.0	78.0	8.6	9.8	32.0	365.0	--
8/22-8/23	2100	81.0	170.0	76.0	159.5	10.0	21.0	11.0	231.0	5.5
8/23-8/24	1100	75.3	82.7	--	--	14.6	16.1	--	--	5.5
8/26-8/27	2280	91.0	220.4	93.4	138.7	10.0	18.8	--	--	--

bumin-globulin ratio of 4.7:2.5. Cholesterol was 266 mg. %. The remainder of the blood chemistry studies are listed in Table 1. ECG was normal. Chest x-ray was normal, with no increase in heart size. Roentgenograms of the bone showed no abnormalities of bone density or texture. Tests with PPD No. 1 and No. 2 were negative. Urinary 17-ketosteroid excretion was normal (3.3 mg/24 hours).

Course.—For several days an attempt was made to raise the serum Na and Cl levels by administration of 4 to 8 gm. of salt in the form of dietary supplements. The oral rather than intravenous route was decided upon, because it was thought to be more physiological and because of the coexistent hypertension. It proved to be unsuccessful, owing to the child's poor oral hygiene and lethargy. During this period the daily oral fluid intake varied between 800 and 1800 ml. The urinary output, initially 1500 to 2000 ml., fell to 600 ml. Since the falling urinary output was considered to be evidence of impending shock and the blood pressure of 150/80 was believed to be below the child's usual range, intravenous infusion of isotonic saline solutions was started. The infusion caused a precipitous rise in blood pressure. This was therefore changed to half-isotonic saline and administered slowly. The blood pressure re-

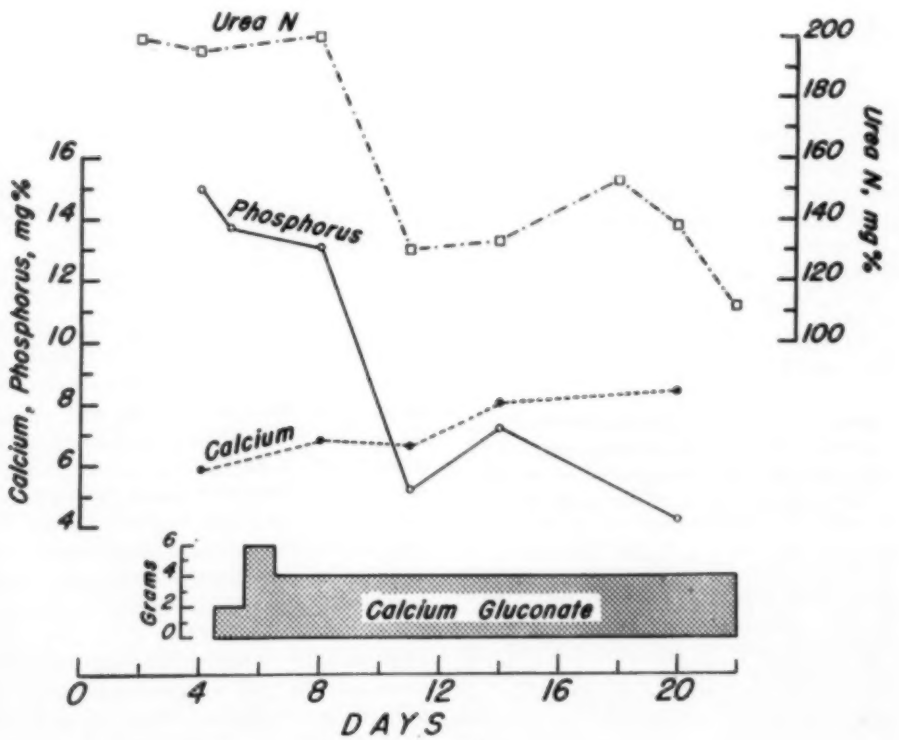

Figure 2

mained at high levels but did not rise further. Over a six-day period the patient received 4 to 12 gm. of salt intravenously per day, in addition to the amount contained in a high-salt diet. He then was maintained on a diet containing 10+ gm. of salt per day, plus 8 additional grams in the form of salt tablets. This regimen raised the serum Na and Cl values from a low of 114 mEq. per liter and 72 mEq. per liter, respectively, to normal levels (Table 1 and Fig. 1). The BUN fell from an initial level of 200 mg. % to 111 mg. % on discharge from hospital and to 53 mg. % on follow-up in the clinic two months later.

The oral fluid intake was unlimited, and the urinary volume ranged between 1100 and 2500 ml. after initiation of this therapy. Urinary Na and Cl concentrations were fairly constant, ranging between 70 and 90 mEq. per liter for both ions. Twenty-four-hour urinary ammonia excretions varied from 0.2 to 0.7 gm. (Table 2).

The child also received 4 gm. of calcium gluconate daily with therapeutic doses of 4000 units of vitamin D. Phosphorus-containing foods (milk, fish, eggs, cheese) were limited, and 4 tablespoonfuls of aluminum hydroxide gel were given daily. These measures with the increase in fluid intake achieved the marked fall in serum phosphorus from 11 mg. % to 3 mg. % (Fig. 2).

The diet prescribed was low in protein. The lowest value which was consistent with palatability by the child was 1 gm. per kilogram per day. With this regimen, the patient was discharged with normal serum electrolytes and in relatively good clinical condition. The child was maintained in this way until clinic contact was lost, in December, 1956. Several transfusions were required during this period of time because of falling hemoglobin, at levels of 6+ gm., and the hematocrit value, at 20%. Serum Na, Cl, and K were maintained at approximately normal levels during his clinic visits (Table 1).

After clinic contact was discontinued, the patient was next heard about from another institution, where he had been admitted on the advice of a private physician to whom he had been taken in search of a more favorable prognosis. Admission took place on Jan. 23, 1957. The patient died within 24 hours. Antemortem laboratory results were serum sodium 127 mEq. per liter, chloride 87 mEq. per liter, CO_2 12.4 mEq. per liter, potassium 8.4 mEq. per liter, calcium 3.6 mEq. per liter, phosphorus 2.0 mEq. per liter, BUN 123 mg. %, Hb. 5 gm. Postmortem examination permission was denied, and the death was considered to be on the basis of chronic renal disease.

Comment

This patient satisfies the proposed criteria of Levere and Wesson for salt-losing nephropathies [9]:

(1) Signs and symptoms consistent with dehydration

(2) Low serum Na and Cl levels on a normal salt intake, relieved by an increased amount of salt—10 to 20 gm. per day

(3) Signs that adrenal steroids are not lacking, i. e., unresponsiveness to desoxycorticosterone acetate (Doca) and normal urinary excretion of 17-ketosteroids

(4) Evidence of renal disease with low urinary specific gravity, polyuria, elevated BUN and serum creatinine, and anemia—all persistent on high salt intake; the urine sediment may be relatively normal

Several interesting aspects of the pathophysiology of this syndrome warrant emphasis. Patients with salt-losing nephropathies have both glomerular and tubular disease. The tubular defect predominates, with impairment in the reabsorption of salt and water. Therefore, the chief laboratory finding is the excessive loss of electrolytes in the urine, with resulting hyponatremia and hypochloremia and all the clinical manifestations of a low-salt syndrome of the depletion type. These patients do not respond to deoxycorticosterone acetate (or to their own aldosterone), and the urinary 17-ketosteroid output is normal, since the basic defect is in the kidney.

Although the amount of filtrate reaching the tubules is markedly decreased, owing to glomerular disease, the syndrome is accompanied by polyuria because the tubular mechanism for obligatory sodium and water resorption is defective. An osmotic diuresis results. Antidiuretic hormone, which is being produced normally, has no effect on the polyuria, as the diseased distal tubules are already working at their maximum reabsorptive capacity against the flood of saline fluid from above.

Secondary to the glomerular disease, these patients tend to accumulate products of cellular metabolism. First, there is an elevation of the BUN, which is further

aggravated by the dehydration. With rehydration the BUN may fall, but seldom to normal values. Secondly, the serum potassium is elevated because of the glomerular pathology. Tissue breakdown and the urinary loss of Na add to the elevated serum K, the latter by evoking an egress of K from the cells as a result of acidosis. Also, phosphates and sulfates are retained, owing to the glomerular defect.

In addition to the above abnormalities, i. e., hyponatremia, hypochloremia, polyuria, hyperkalemia, and retention of the acid metabolites, acidosis is also present. This acidosis is a result of the renal tubular impairment in the formation of acid urine and ammonia, which leads to defective base conservation. Because these tubular mechanisms are impaired, the acid radicals in the urine are necessarily accompanied by large amounts of fixed base, such as sodium, potassium, and calcium. Serum calcium was low; however, clinical tetany was prevented because of the associated acidosis.

Another interesting aspect of the pathophysiology of this condition is the concept of limitation of flexibility and the retarded compensatory mechanism of the kidney.[15] As can be seen from Figures 1 and 2, the saline infusions were started 24 to 48 hours before the serum determinations returned toward normal values. The rate at which diseased kidneys adjust serum electrolytes is slower than normal.[13]

Therapeutic Regimen.—With some understading of the basic pathophysiology of the disease, a therapeutic regimen can be outlined. It was necessary to add large quantities of salt to the diet. The optimum intake of salt was determined by attempting to vary the amounts from day to day and observing the child's clinical condition and laboratory data. In this child, it was necessary to initiate therapy with intravenous infusions of half-isotonic saline, despite the hypertension, since he was unable to keep up, via oral means, with his urinary output of salt. Between 6 and 16 gm. of supplemental salt, over and above liberal amounts present in the diet, were needed to keep the serum electrolyes in the normal range.

The diet contained adequate calories to prevent abnormal endogenous protein catabolism. The exogenous protein intake was limited to 1 gm. per kilogram per day. This was the lowest level that could be maintained without causing the patient to lose interest in his meals. It has been reported that by limiting the protein even further the mental outlook of the patient could be improved by further reducing the BUN.[16]

Fluid intake was no problem, as the thirst mechanism insured adequate amounts to cover the salt intake.

Phosphorus-containing foods were reduced from the diet, and aluminum hydroxide gel was given to reduce the intestinal assimilation of any available phosphorus. Calcium gluconate was given orally, in order to maintain positive calcium balance.

The acidosis present was not promptly corrected, since this state helped prevent clinical tetany by almost completely ionizing the available calcium. Potassium-containing foods were limited until such time as it became evident from the trend in serum potassium levels that the patient was able to handle the normal dietary potassium.

Frequent blood transfusions were necessary to maintain the hemoglobin level and prevent symptoms of anemia from developing. Cobalt has been reported to be of benefit in the anemia of uremia, but, because of the reports of hypothyroidism from prolonged use and the metallic taste that results, it was not used.

With this therapeutic regimen our patient was rehabilitated and maintained at a functional capacity for six months. He was able to attend school during this period.

Summary

The case of the youngest patient with salt-losing nephritis is reported. Pathophysiology is explored. Therapeutic regimen is discussed. The case is unusual in that hypertension was present from the onset.

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Progress in Pediatrics

ECHO Type 9 Virus Disease

Virologically Controlled Clinical and Epidemiologic Observations During 1957 Epidemic in Milwaukee with Notes on Concurrent Similar Diseases Associated with Coxsackie and Other ECHO Viruses

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Large numbers of febrile illnesses associated with a great variety of clinical manifestations occur among children and adults each summer and autumn in temperate zones. There is increasing evidence that the family of enteroviruses,[1] comprising the polioviruses, Coxsackie, and ECHO viruses, are responsible for a large proportion of these seasonal diseases. Since we already know of 51 antigenically distinct types in the family of enteroviruses, with more candidates awaiting their turn for admission, it seems highly desirable to learn of the clinical and epidemiologic potentialities of each virus. Such information can best be obtained during epidemics caused predominantly by one virus, and then only with clinical and epidemiologic data based exclusively on virologically proved cases. The present communication contains the results of such a study of an epidemic of ECHO Type 9 virus disease during the summer of 1957 in the city of Milwaukee, with an estimated population of 740,000.

History of ECHO Type 9 Virus

The first strains of ECHO 9 virus, originally designated as HE (human enteric) Type 3, were recovered from healthy children during epidemiologically quiescent periods in Cincinnati and Mexico and represented only a small proportion of the large number of enteroviruses that were isolated.[2,3] At the end of 1955, when this virus was renamed ECHO 9 by the Committee on ECHO Viruses,[4] there was only a single strain, from a patient with the aseptic meningitis syndrome in West Virginia. The importance of this virus as a cause of large epidemics of aseptic meningitis and febrile illnesses with rash did not become apparent until hundreds of strains recovered in 1956 from patients in Belgium and Holland,[5] Britain,[6,7,7a] Germany,[8,9] Sweden,[10] Denmark,[11] Switzerland,[12] and Canada [13] were reported as being serologically similar to ECHO 9. Viruses recovered during the course of small outbreaks in Britain [7] in 1954 and 1955 and those recovered during an extensive outbreak in Italy [14] in 1955 have also been identified [15] as being related to ECHO 9. Many of the clinical and epidemiologic reports of outbreaks cannot be used for defining the clinical and epidemiologic spectrum of ECHO 9 virus disease because of the untested assumption that all of the clinical manifestations observed during the outbreaks were caused by the same etiologic agent. While frequent occurrence of exanthem was a common finding in the Canadian and most European epidemics of 1956, no exanthem was observed during the extensive epidemic

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in Italy [14] in 1955 or in an epidemic in a Swiss village [12] in 1956, and it is possible that the kind and incidence of clinical manifestations may vary with different strains of the virus. The high incidence of virus isolations from the cerebrospinal fluid [5,11,14] clearly indicated the role of this virus in the aseptic meningitis syndrome, but the suggestions that it might also be the cause of mild transitory paralysis [12] or of other forms of severer involvement of the central nervous system [14] required more detailed studies to exclude other etiologic factors. Verlinde's [10] demonstration of ECHO 9 virus in a concentration of approximately 1,000,000 infective doses per gram in the medulla of an 8-month-old infant, who died within 24 hours after onset of a febrile, comatose illness, indicated how extensively this virus may multiply in the human nervous system.

Recognition of Milwaukee Epidemic and Plan of Present Study

Prior to the end of June only two cases of paralytic poliomyelitis had been reported for 1957 to the Milwaukee Health Department—one with onset on Jan. 28 and the other on June 15. Between the last week of June and Aug. 11 more than 80 patients from Milwaukee and surrounding communities had been admitted to the Johnston Municipal and Milwaukee Children's hospitals with a tentative diagnosis of poliomyelitis. With only few exceptions there was not even questionable paralysis. Some of the patients exhibited a rash, and others stated that children in their households had recently suffered from febrile illnesses with rash. At the same time, public health nurses reported seeing many children with acute febrile illnesses, often with rash, and physicians were making frequent diagnoses of measles (rubeola) and German measles (rubella). Attempts by Dr. Henry J. Wisniewski, of the Milwaukee Health Department laboratory, to recover a virus in HeLa-cell cultures from more than 40 stools of hospitalized patients yielded entirely negative results. All of these observations suggested that poliovirus was not significantly involved in this outbreak. When stool specimens from the same patients were tested in monkey kidney tissue cultures in the Cincinnati laboratory, more than 80% yielded cytopathogenic agents, which, with few exceptions, were quickly identified as being serologically related to ECHO 9.

The objectives of the subsequent studies may be listed as follows:

1. Determine the spectrum of clinical manifestations of infection with ECHO 9 virus by virologic studies on hospitalized patients exhibiting the aseptic meningitis syndrome, all degrees of paralysis, encephalitis, polyneuritis, or other obscure neurologic manifestations, as well as by studies on entire families in which acute febrile illnesses of unknown etiology were occurring.

2. Obtain an estimate of the total incidence of both clinically recognizable and inapparent ECHO 9 infection as well as of its mode of spread in the community by virologic studies on families with and without acute febrile illnesses of unknown etiology and by surveying an adequate sample of the population to determine the proportion exhibiting such illnesses during a specified period of time.

3. Learn something of the sources of infection by quantitative studies on the presence of virus in the nose, mouth, throat, and feces and on the persistence of virus excretion during convalescence.

Materials and Methods

Specimens from Patients and Family Study Groups.—Cerebrospinal fluids and stool specimens obtained from patients at the Johnston Municipal Hospital and at the Milwaukee Children's Hospital * were kept in "deep freeze" compartments at −10 to −20 C for varying periods of time before being shipped in the frozen state with dry ice to the Cincinnati laboratory. Stool specimens from the family study groups were picked up from the homes within 20 hours and similarly frozen and shipped. Acute- and convalescent-phase serum

* Specimens from Milwaukee Children's Hospital were provided by Dr. J. C. Peterson.

specimens on many of the patients were similarly stored and shipped.† Upon arrival in Cincinnati all specimens were stored in a deep freeze at about —20 C. Tests on a number of stool extracts stored in an ordinary refrigerator at 5 C for seven days revealed no significant loss in titer of ECHO 9 virus, and one can expect, therefore, that the method of handling the specimens resulted in little or no loss of virus except where the amounts might have been minimal to begin with.

Isolation and Identification of Viruses.—Whenever enough stool was present, 2 gm. from each specimen was ground with 18 ml. of Earle's solution, containing 2000 units of penicillin, 2 mg. of streptomycin, and 25 units of nystatin (Mycostatin) per milliliter. The stool suspensions were allowed to settle in the refrigerator for one or more hours, and 10 to 12 ml. of the supernatant liquid was then centrifuged on a horizontal centrifuge at 2000 rpm for 30 minutes. The supernatant liquid was frozen for several hours or overnight in a deep freeze at about —20 C. The final step involved centrifugation of the frozen and thawed liquid at 10,000 rpm for 30 minutes in the refrigerated, vacuum Spinco ultracentrifuge (No. 40 rotor). The clear supernatant liquid, when acid, had its pH adjusted to about 7.6 to 8.0 with a few drops of a 4.4% solution of $NaHCO_3$ and was added to each of three tissue-culture tubes in 0.2 ml. amounts. When enough cerebrospinal fluid was available 0.5 ml. amounts were added to each of three or four tissue culture tubes.

Only Cynomolgus monkey kidney tissue cultures were used in these tests. One-half milliliter amounts of a 1:200 suspension of the washed trypsinized cells in a medium consisting of 0.5% lactalbumin hydrolysate in Hanks' solution and 2% heated calf serum were allowed to grow in stationary roller tubes until the medium became acid—usually four days. At that time each tube received 1.5 ml. of the same medium plus additional $NaHCO_3$ to a final concentration of 0.07%, and the tubes were ready for use two to three days later. Prior to inoculation, the old medium was removed and replaced with 2 ml. of 0.5% lactalbumin hydrolysate in Earle's solution (without serum), gassed with CO_2 to a pH of about 7.5 to 7.6. No further change of medium or adjustment of pH was required during the subsequent eight-day period of observation. After inoculation the tubes were kept in a roller drum. No blind passages were carried out—all viruses listed in Tables 2 and 3 were recognized by a cytopathogenic change in the first cultures. The cytopathogenic effect of the ECHO 9 and Coxsackie viruses, as a rule, showed up within two to four days, except when minimal amounts were present in the specimens. The other ECHO viruses listed in the Tables usually showed up later, and the two untypable strains required one or more passages before a complete cytopathogenic effect was obtained. When the cytopathogenic effect was complete in the first culture fluids, they were used for identification by means of neutralization tests with 3 types of poliovirus, 19 types of ECHO virus, and 6 types of Coxsackie virus antisera, as recommended by the Committee on Enteroviruses.[3] After it appeared that approximately 90% of the cytopathogenic agents were related to ECHO 9 virus, all strains producing a compatible cytopathogenic change were first screened with ECHO 9 antiserum. The culture fluid, used in a final dilution of 10^{-1}, usually contained more than 100 TCD_{50} (tissue-culture-infective doses) per 0.2 ml. (frequently 10^2 to 10^3), and the antiserum, with a titer of 1:16,000 to 1:32,000 per 0.1 ml. vs. 10^2 to 10^3 TCD_{50} of the prototype "Hill" strain of ECHO 9 virus, was used in an original dilution of 1:100. Neutralization was clearly evident in the readings made two days after inoculation of the serum-virus mixtures in the tubes, but in most instances, especially with the larger doses of virus, not at four days and eight days. This not only indicated the importance of early readings for the identification of these viruses but also suggested that the Milwaukee ECHO 9 strains were either antigenically somewhat different from the prototype virus or were inherently more difficult to neutralize. In quantitative tests vs. 10^2 to 10^3 TCD_{50}, the prototype ECHO 9 antiserum was found to have 10 to 100 times lower titers against Milwaukee strains.

Serologic Tests.—Neutralization tests were carried out in tissue-culture tubes, and the results were determined by the presence or absence of a cytopathogenic effect. Here, also, it was deemed essential to have early and late readings. Although many of the Milwaukee strains yielded culture fluids with infective titers in the range of 10^3 TCD_{50}, these fluids contained only 2 to 4 complement-fixing units per 0.2 ml. and, because of the anticomplementary character of the undiluted culture fluids, complement-fixation tests could be carried out with only minimal amounts of antigen.

Results

Viruses Recovered from Hospitalized Patients.—There were 213 patients (149 from the city of Milwaukee) who were admitted to the Johnston Municipal and Milwaukee Children's hospitals between June 1 and the end of September,

† Dr. Henry J. Wisniewski, of the Milwaukee Health Department Laboratory, processed and shipped these specimens.

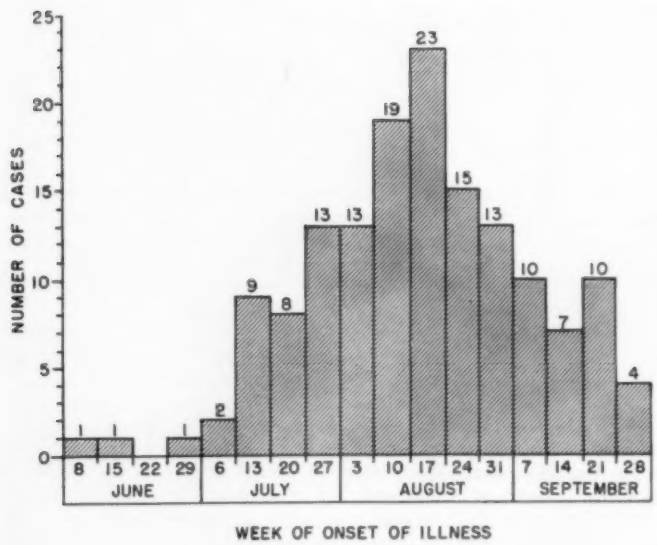

Fig. 1.—Week of onset of illness in 149 Milwaukee residents hospitalized for suspected viral infections of central nervous system.

1957, because their physicians originally suspected some form of poliomyelitis—nonparalytic, paralytic, or "encephalitic." Figure 1 shows the time sequence by week of onset during which the illnesses occurred among the Milwaukee residents, and Table 1 shows the age and sex distribution. Specimens from 152 patients were tested in monkey kidney tissue culture: stools and cerebrospinal fluid from 62, stools only from 69, and cerebrospinal fluid only from 21. The results obtained in 136 patients who exhibited the aseptic meningitis syndrome, with or without paralytic or encephalitic manifestations, are presented in Table 2. Excluded from this tabulation are 14 patients who had bacterial meningitis, cerebrovascular accident, mumps, bacterial tonsillitis, or dubious and indefinite illnesses without pleocytosis, from whom no viruses were recovered, and 2 infants with fatal

TABLE 1.—*Age and Sex Distribution of 149 Residents of Milwaukee Hospitalized for Suspected Viral Infections of the Central Nervous System*

Age, Yr.	Sex *	Cases, No.
Under 6/12	M	4
	F	1
6/12–4	M	21
	F	12
5–9	M	30
	F	15
10–14	M	21
	F	7
15–19	M	5
	F	3
20–29	M	13
	F	10
30–39	M	4
	F	2
40 and over	M	0
	F	1

* Note high ratio of males to females in children under 15 years of age.

TABLE 2.—*Viruses Recovered from Hospitalized Patients Exhibiting Aseptic Meningitis Syndrome and Occasionally Also Signs of More Extensive Involvement of Central Nervous System*
Milwaukee, End of June to End of September, 1957

		Cases, No.
Patients with stools or CSF or both tested for virus		136
Virus in monkey kidney tissue cultures		101 (74%)
ECHO 9 virus	90	
Other ECHO viruses	5	
ECHO 2	1	
ECHO 14	1	
ECHO 16	2	
ECHO 18	1 *	
Coxsackie A 9 (CSF)†	1	
Coxsackie B viruses	4	
B3	1 (CSF)	
B 4	1 (CSF)	
B 5	2 (1 CSF)	
Poliovirus (Type 3)	1	

* This patient also exhibited a concurrent rise in complement-fixing antibody for mumps virus.
† CSF indicates that the virus was recovered from the cerebrospinal fluid.

illnesses that will be described separately. Cytopathogenic viruses were recovered from 101 of the 136 other patients. In 30 patients virus was recovered from the stool as well as from the cerebrospinal fluid, and in each instance the same virus was present in both materials. ECHO 9 virus was recovered from 90 patients. Cerebrospinal fluid specimens were available from 51 of these 90 patients, and 40 yielded the virus. Among 42 ECHO 9 patients with both stool and cerebrospinal fluid available for test, the virus was recovered from both materials in 26, from the stool but not from the cerebrospinal fluid in 11, and from the cerebrospinal fluid but not from the stool in 5.

Three of the 4 other types of ECHO virus (Types 2, 14, and 16) have previously been found by others in association with the aseptic meningitis syndrome. It is noteworthy that, among the five patients who yielded Coxsackie viruses, the viruses were recovered from both the cerebrospinal fluid and the stools in the four patients from whom both materials were available. These cytopathogenic Coxsackie viruses have all previously been shown by others to be associated with aseptic meningitis syndrome. The one strain of poliovirus recovered during the entire study was obtained at the end of September from a 41-year-old woman with definite paralysis who had previously received two doses of Salk vaccine.

Among the 35 patients from whom no virus was recovered there were two with a clinical diagnosis of definite paralytic poliomyelitis (one of them had received Salk vaccine) who developed no antibody for ECHO 9 virus, and the poliovirus antibody tests provided evidence of a Type 1 poliovirus infection in one and a possible but not definite Type 2 poliovirus in the other (high titers of antibody were present in both serum specimens only for Type 2, but the first serum specimen was obtained 10 days after onset of symptoms). There were also two patients who, without any history of exposure to mumps and without exhibiting signs of parotitis, developed antibody for mumps virus but not for ECHO 9. Most of the remainder were probably also infected with ECHO 9 virus; in several instances the virus was recovered from siblings and of 11 patients on whom acute and convalescent phase sera were available only 2 had no ECHO 9 antibody (7 of the others showed a significant rise, and 2 had high titers in the first specimen without further rise).

It is thus evident that approximately 90% of the hospitalized patients with evidence of viral infection of the nervous system were affected by ECHO 9 virus and that at least 9 other distinct enteroviruses were playing minor roles during the same period of time.

Viruses Recovered from Families With and Without Acute Febrile Illnesses.—Between Aug. 14 and Aug. 20 a total of 2447 households containing 11,403 persons were visited by 108 public health nurses. The nurses found 62 families in which one or more members had a current acute febrile illness. Physicians visited 53 of these families, obtained epidemiologic and clinical histories, and examined each member of the family who was home at the time of their visit. It was from among these families that stool specimens were obtained for examination. These families were revisited in September to check on the subsequent development of illness among those who were well at the time of the first visit. During the same period cooperation in supplying stool specimens was obtained from 25 families in which there were no febrile illnesses during the 30-day period immediately preceding the nurse's visit. Between Aug. 14 and Aug. 21 stool specimens were obtained from 107 of the 130 members in the 25 control families. On Aug. 26 each of these 25 families was revisited by a public health nurse to ascertain whether a febrile illness had occurred during the interval, and none was found. The geographic distribution of

Geographic Distribution of Families
Sampled for Virus Aug. 14-21, 1957
in City of Milwaukee
With Acute Febrile Illness
Without " " "

Figure 2

the families with and without illness is shown in Figure 2.

The results of the tests for virus, shown in Table 3, are as follows:

(*a*) Viruses were recovered from 92% of the families with acute febrile illnesses and from only 28% of those without illness.

(*b*) A total of 58 ECHO 9 viruses were recovered from 104 persons in 22 families with illness, and only 1 ECHO 9 virus was recovered from 107 persons in the control group, and that was derived from a 21-month-old baby, in whom signs of illness may have been missed.

TABLE 3.—*Viruses Recovered from Families With and Without Acute Febrile Illnesses* *
Milwaukee, Aug. 14 to 21, 1957

Category	Families Tested, No.	Families Yielded Virus, No.	Families Yielded ECHO 9, No.	Persons Tested, No.	Viruses Isolated, No.	ECHO 9, No.	Coxsackie A 9, No.	Other Viruses
Illness compatible with ECHO 9	26	24 (92%)	22 (85%)	104	66	58	5	3 †
No current illness	25	7 (28%)	1 (4%)	107	10	1 ‡	0	9 §

* A single stool specimen from each person was tested in monkey kidney tissue culture.
† The single isolation of ECHO 9 virus in the control group was from a 21-month-old baby; they are related to ECHO 16. The third virus was Coxsackie B 5 and occurred in a family in which six other persons yielded ECHO 9.
‡ Two of these viruses were isolated from ill children (one with rash) in the same family.
§ These nine viruses consisted of the following: Coxsackie B 4, four strains; ECHO 14, two strains; ECHO 18, one strain; untypable ECHO, two strains.

(*c*) In one of the families, in which all seven children were ill—three of them with rash—the stool specimens from five children, including the three with rash, all yielded Coxsackie A 9 virus (Fig 3), which was not recovered from any of the control families but was isolated from the cerebrospinal fluid and stools of one of the hospitalized patients with the aseptic meningitis syndrome.

(*d*) In another family, in which both children were ill, one of them with rash, Type 16 ECHO virus was recovered from both, and this type was not encountered in the control group. The ECHO 16 virus recovered from this family as well as the strains recovered from two hospitalized patients with aseptic meningitis (Table 2) are only partly related to the prototype "Harrington" strain, and failed to be identified in the original test with 40 units of the prototype monkey antiserum. The titer of the prototype antiserum was approximately 300 times lower for the Milwaukee strains than for the prototype, "Harrington" strain.

(*e*) With one exception, all members of the same family were found to carry the same type of virus; the exception was a Coxsackie B 5 recovered from one child of a family in which six other members yielded ECHO 9 virus.

(*f*) Nine of the ten viruses recovered from the control group of families without illness were not encountered among the families with illness; the four strains of Coxsackie B 4 derived from two families (two children in each) indicate that this virus often produces inapparent infection, and it is noteworthy that it was encountered only once among the hospitalized patients with the aseptic meningitis syndrome; the same may be said of the ECHO 14 virus, two strains of which were encountered in two healthy children in one family and one among the hospitalized patients; the one strain of ECHO 18 virus was recovered from a healthy 7-year-old child (this type of virus has thus far been associated with disease only in infants under 1 year of age [17,18]) and was also recovered from the stools of a 5-month-old baby that died in Milwaukee in September, 1957; the two untypable ECHO viruses, distinct in their properties from the others encountered during the course of this study, were recovered in two separate families—one from a 6-year-old boy in a family of four and the other from a 47-year-old woman in a family of five. These two strains also could not be typed with antisera against the recently established ECHO types 20 to 24 viruses. They are not pathogenic for newborn mice.

(*g*) Since not a single strain of poliovirus was found among the 76 cytopathogenic agents recovered from the 51 families, it would appear that, along with many of the other enteroviruses, the polioviruses were largely "pushed off the track" during the course of this predominantly ECHO 9 epidemic.

The chief conclusion to be drawn from these data is that during the course of this epidemic the ECHO 9 virus was closely associated with families exhibiting acute

TABLE 4.—*Incidence of Illness, Rash, and Healthy Virus Carriers Among Persons of Different Age in Twenty-Two Families with ECHO 9 Virus Infection*

Age, Yr.	Total No. Tested for Virus	Persons in Indicated Category, No.						Virus Recovery from Ill Persons
		ECHO 9 in Stools	Illness + Rash	Illness, No Rash	Healthy Virus Carriers	Total Ill & Healthy Carriers	No Illness, No Virus	
0–4	35	31	27 (77%)*	2	6† (17%)*	35	0	25/29 (87%)
5–15	21	14	7 (44%)*	8	1 (6%)*	16	5‡	13/15 (87%)
Over 15	33	13	1 (6%)*	12	3 (19%)*	16	17§	10/13 (77%)
All ages	89	58	35 (52%)*	22	10 (15%)*	67	22	48/57 (84%)

* Per cent of total ill and healthy carriers.
† One of these children developed a "compatible" illness 20 days after ECHO 9 virus was recovered from her stool, but no tests were carried out during the course of the illness.
‡ One of these children developed a "compatible" illness nine days after her virus-negative stool, but no tests were carried out during the course of the illness.
§ Three of these persons (aged 27, 29, and 33 years) developed "compatible" illnesses 2, 12, and 12 days, respectively, after their virus-negative stools, but no tests were carried out during the course of their illnesses.

febrile illnesses. The data presented in Table 4 indicate the incidence of illness, rash, and healthy virus carriers among persons of different age in the 22 families with ECHO 9 virus infection. If we assume that all compatible febrile illnesses occurring at about the same time in these households were caused by the same virus, the incidence of virus recovery from the stools of ill persons was 87% in the 0- to 4- and 5- to 15-year age groups and 77% in those over 15 years of age (84% for the entire group). The stools without virus were with one exception obtained three to six days after onset of illness. It may be seen that among the 35 children in the 0- to 4-year age group 29 had various clinical manifestations and 6 were healthy virus carriers; among the 21 in the 5- to 15-year age group, 15 were ill and 1 was a healthy virus carrier, while among the 33 older persons (with one exception parents over 20 years of age), at least 13 were ill and 3 were healthy virus carriers. It is clear from these data that the incidence of those with no illness and no virus in their stools increases with increasing age and that most of those under 15 years of age were susceptible; in the older age group there were 52% (17 of 33) or perhaps only 42% (14 of 33, if we count those who developed a compatible illness within 12 days after their stools were tested) who did not become ill or carry virus. Tests on sera of Milwaukee residents, aged 16 to 43 years, obtained prior to the 1957 epidemic (to be described later) indicated that 57% had no antibodies for either the prototype or 1957 Milwaukee strains of ECHO 9 virus. This close correspondence between the expected incidence of immunity and the observed absence of illness and virus carriers in the older age groups suggests that most of these persons were actually immune rather than merely uncontaminated by the virus. It is also noteworthy that among the 19 families from which stools were obtained from either or both parents, the mother or father or both were ill in 10 (both parents being ill in 3 of them).

The data shown in Table 4 indicate that approximately 85% of ECHO 9 virus infections are associated with clinically recognizable illness. An analysis of the dates of onset of clinically manifest illness among persons of different ages in families with multiple cases of ECHO 9 virus disease indicates that in each instance a preschool-age child was the first to become ill. Very young infants and older children and parents developed their illnesses after intervals of 2 to 20 days, usually 3 to 7 days (see Table 5). If the incubation period of a disease is defined as the interval between acquisition of virus and appearance of illness, it is evident that the data in Table 5

TABLE 5.—*Relation Between Dates of Onset of ECHO 9 Virus Disease in Families and Age of Persons*

Family	Person	Age, Yr.	Date of Onset	Virus in Stools	Date of Stool Specimen
1	Child 1	5	8/8	+	8/17
	Child 2	9/12	8/12	+	8/17
	Mother	36	8/12	+	8/17
	Father	37	8/14	+	8/17
	Child 3	9	8/16	+	8/19
2	Child 1	4	8/11	+	8/16
	Child 2	2	8/14	+	8/16
	Mother	26	8/21	+	8/16
	Father	38	Well	0	8/16
3	Child 1	5	8/12	+	8/19
	Child 2	9	8/15	+	8/19
	Father	33	9/1	0	8/20
	Mother	33	Well	0	Not tested later 8/19
4	Child 1	5	8/6	+	8/16
	Child 2	2	8/8	+	8/16
	Mother	33	8/12	+	8/16
	Father	36	Well	0	8/15
5	Child 1	4	8/14	+	8/19
	Child 2	3	8/16	+	8/19
	Father	32	8/17	+	8/19
	Child 3	2	Well	+	8/19
	Child 4	8/12	Well	+	8/19
	Mother	36	Well	0	8/19
6	Child 1	5	8/4	+	8/15
	Child 2	2	8/4	+	8/15
	Mother	31	8/6	+	8/15
	Father	32	8/12	+	8/13

can only suggest but not define the incubation period, for it is possible to acquire the virus before the onset of illness in the index case as well as at various intervals after onset. The data suggest, however, that the children in the 3- to 6-year age group are especially important in introducing ECHO 9 virus into families.

Clinical Picture Exhibited by Hospitalized Patients with Confirmed ECHO 9 Virus Disease

With only few exceptions, to be described separately, the hospitalized patients with confirmed ECHO 9 virus disease exhibited an uncomplicated aseptic meningitis syndrome that in former years would have been reported as nonparalytic poliomyelitis.

Characteristics of the Aseptic Meningitis Syndrome in ECHO 9 Virus Disease.—The incidence of various signs and symptoms recorded on 75 patients of different ages from whom ECHO 9 virus was isolated is listed in Table 6. The disease began with a rise in temperature up to a level of 101 to 103 F on the first day. About 15% of the patients had moderate chills. At the onset the patients usually complained of malaise, irritability, and some degree of weakness. Headache, usually described as very severe and localized in the frontal region, was a complaint in all but 2 of the 75 patients, and these 2 were too young to provide a history. Headache was the first

TABLE 6.—*Symptoms and Signs in Seventy-Five Patients at Johnston Municipal Hospital from Whom ECHO 9 Virus Was Recovered*

	Age, Yr.									
	0–4		5–9		10–19		20 & Over		All Ages	
Symptoms & Signs	No.	%	No.	%	No.	%	No.	%	No.	%
Fever	11	100	16	100	28	100	20	100	75	100
Headache	9	82	16	100	28	100	20	100	73	97
Vomiting	7	64	13	81	17	61	4	20	41	55
Nonexudative pharyngitis	9	82	13	81	16	57	11	55	49	65
Pain in neck	7	64	11	69	21	75	16	80	55	73
Pain in back	2	18	9	56	10	36	13	65	34	45
Abdominal pain	3	27	5	31	5	18	0	0	13	17
Rash	5	45	5	31	2	7	3	15	15	20
Conjunctivitis	1	9	1	6	5	18	3	15	10	13
Cervical lymphadenopathy	4	36	11	69	9	32	6	30	30	40
Nuchal rigidity	6	55	7	44	19	68	13	65	45	60
Vertigo	0	0	3	19	3	11	1	5	7	9
Kernig	2	18	3	12	5	18	0	0	9	12
Brudzinski	2	18	2	12	2	7	0	0	6	8
Babinski	0	0	1	6	2	7	0	0	3	4

symptom noted by 24 of the 75 patients. Some patients with headache were unaware of fever, even though an elevated temperature was found on admission to the hospital.

About 25% of the patients were ill with self-recognized fever and headache for one or two days and then felt well for a period of one-half to two days, after which the original symptoms returned. A few of the patients in this group entered the hospital during the third of a series of such periods of self-recognized recurrence of symptoms. Three patients gave a history of illness lasting three to seven days, feeling well six to nine days, and then having a recrudescence during the course of which they were hospitalized; the recrudescent febrile period lasted four to five days.

The temperature was usually continuously or intermittently elevated for from 2 to 15 days, the median number being 6. These data are based on the number of days the patients indicated they were febrile prior to hospitalization and the number of days in the hospital that the temperature was recorded as exceeding 99 F. The maximum oral temperature recorded in the hospital was 103 F. The maximum temperature exceeded 102 F in only about 25% of these patients; it was 101.2 to 102 F in about 50%, and in the remainder it did not exceed 101 F.

Vomiting occurred in 60% to 80% of the patients under 20 years of age and in only 20% of those aged 20 or more. Projectile vomiting was noted in two adults. Six patients who did not vomit complained of nausea. Abdominal pain was a complaint in 27% to 31% of children under 10 years of age, in 18% of those aged 10 to 19, and in none of those aged 20 or over. Diarrhea was not a feature of the disease, and a substantial number of the patients were constipated.

Mild to moderate nonexudative pharyngitis, usually but not always associated with subjective soreness of the throat, was observed in 82% of the children under 10 years of age and in 57% and 55% of those aged 10 to 19 and 20 or over, respectively. Coryza was not present in any of the patients. Cough was not a feature of the disease, and in the six patients who stated that they had occasional mild cough it might have been the result of the existing pharyngitis. The cervical lymph nodes were noted as being palpable in 40% of the patients of all ages (69% in the 5- to 9-year group), but these were usually small and either nontender or only slightly tender. No enlargement of the postauricular or suboccipital lymph nodes occurred.

Pain in the neck was a symptom in 64% to 80% (73% in patients of all ages) and back pain, in 18% to 65% (45% in patients of all ages). Both neck and back pain occurred more frequently among adults. Nuchal rigidity was found in only 60% of all patients, the neck being supple in some patients who complained of neck pain. There was no correlation between the presence or absence of nuchal rigidity and the degree of pleocytosis; in some patients without nuchal rigidity the number of leukocytes in the cerebrospinal fluid exceeded 500 per cubic millimeter. The Kernig and Brudzinski signs were only rarely encountered (12% and 8%, respectively); these signs were noted only in children and were only transiently present. Prior to being discharged from the hospital 70 of these patients were examined, usually on the sixth hospital day, by physical therapists with long experience in evaluating muscle power in patients with poliomyelitis. Some degree of spasm of the erector muscles of the neck was noted in 54 and of the thoracic or lumbar erector muscles, in 48 patients. The degree of spasm in the cervical muscles was recorded as severe in only three patients and in the thoracic or lumbar muscles, in only nine patients, and in these patients the spasm persisted over a prolonged period. Among five of these patients examined by a neurologist (Dr. Jean Davis) 6 to 10 weeks after discharge from the hospital, one still

had severe spasm of the erector spinae group of muscles and four had slight to moderate spasm; two of these patients had weakness of the abdominal muscles, apparently secondary to the spasm of the erector spinae muscles. None of the patients had flaccid paralysis, and none died.

The following other manifestations were encountered with a low frequency: There were 10 patients who complained of pain on movement of the eyes; 8, of pain in the legs; 7, of vertigo, often severe; 3, of pain in the chest; 3, of pain in the wrist or knee joints; 2, of pain in the shoulder region, and 1, of pain in the arms.

Rash was noted in 45% of the hospitalized children under 4 years of age, as compared with 77% among children with ECHO 9 virus disease studied in the homes. However, of the 11 children of this age group in the hospital only one was less than 3 years of age, while 17 of the children in the homes were less than 3 years old, and 16 of the latter had rash, indicating that the highest incidence of rash is in this youngest age group. The characteristics of the rash as seen in both hospitalized and home patients will be described later.

The spleen was not palpable in any of the patients, and the liver was noted as extending 1 to 2 cm. below the costal border in only three patients, aged 3 to 7 years. Enlargement of the spleen was recorded in 33% of patients during the course of an epidemic in 1955 in Italy.[14]

Signs of More Extensive Involvement of Central Nervous System in ECHO 9 Virus Disease.—Signs indicative of more extensive involvement of the central nervous system were observed in six virologically proved cases.‡ Choreiform, jerking, and undirected random movements of all extremities; right facial weakness, and general facial grimacing were transiently present in a one-month-old baby. Coma and choreiform movements were noted in a 10-year-old girl. Loss of balance associated with the ataxic gait and tendency to fall to the right appeared 2 days after onset and persisted for 10 days in a 22-month-old baby. Another patient, who complained of vertigo and inability to walk without stumbling or falling, exhibited horizontal nystagmus for a period of a few days. These manifestations, taken together with complaints of vertigo in at least six other patients, suggest the possibility that the vestibular nuclei in the medulla may be affected in ECHO 9 virus disease. A clinical diagnosis of mild bulbar poliomyelitis was recorded on a 9-year-old boy, who had received three doses of Salk poliomyelitis vaccine and who exhibited a transitory nasal voice with diminished gag and cough reflexes. A diagnosis of spinal paralytic poliomyelitis was initially made on a 20-year-old woman who had received two doses of Salk vaccine and who exhibited weakness and *dizziness* on standing, was unable to do "sit-ups," and had enough spasm of the back muscles and weakness of the hips to require crutches for getting about for a period of about two months. In the last two patients no poliovirus could be detected in the stools in the presence of ECHO 9 antiserum.

Clinical Laboratory Findings.—The clinical laboratory tests on the cerebrospinal fluid and blood of patients from whose CSF or stool ECHO 9 virus was isolated are summarized in Table 7. There was great variation in the extent of pleocytosis. In three instances the number of cells was less than 10 per cubic millimeter, the minimal number usually accepted as abnormal. However, ECHO 9 virus was isolated from both the CSF and stool of a 16-month-old infant whose CSF cell count was only 5 per cubic millimeter—1 polymorphonuclear leukocyte and 4 lymphocytes. In a 3-year-old child, with fever, rash, headache, and pain in neck and back but without nuchal rigidity, the CSF on the fourth day of illness had only 3 cells per cubic millimeter and virus was recovered

‡ Dr. J. C. Peterson provided some of the following observations.

TABLE 7.—*Results of Clinical Laboratory Examinations on Cerebrospinal Fluid and Blood from Patients at Johnston Municipal Hospital from Whom ECHO 9 Virus Was Recovered*

Cerebrospinal Fluid								Blood			
Cells/ Cu. Mm. No. 1	No.	Total Protein, Mg. %	No.	Sugar, Mg. %	No.	Chlorides, Mg. %	No.	White Cells/ Cu. Mm.	No.	Sedimentation Rate,* Mm. in an Hr.	No.
0-9	3	15-24	1	40-49	2	670-679	1	3,000-3,999	5	0-4	3
10-49	9	25-34	10	50-59	27	680-689	5	4,000-4,999	8	5-9	5
50-99	14	35-44	13	60-69	25	690-699	13	5,000-5,999	17	10-14	10
100-199	14	45-54	14	70-79	5	700-709	13	6,000-6,999	11	15-19	13
200-499	8	55-64	11	80-89	0	710-719	11	7,000-7,999	15	20-24	12
500-999	15	65-74	5	90-99	1	720-729	7	8,000-8,999	10	25-29	10
1,000-1,999	9	75-84	2			730-739	3	9,000-9,999	4	30-34	7
2,000 & over	3	85 & over	6			740-749	1	10,000 & over	3	35 & over	8
Total	75		62		60		84		73		68
Lowest values	0		16		46		670		3,150		2
Highest values	2,640		115		98		740		12,300		43

* Wintrobe-Landsberg method.

from the stool but not from the CSF. In the third patient, an 11-year-old, with fever, headache, pain in the back, and nuchal rigidity, no cells were found in the CSF; virus was recovered from the stools, but the CSF was not available for test. Although this patient had the clinical signs of the aseptic meningitis syndrome, the diagnosis could not be supported by the CSF findings. It is noteworthy that this patient's mother and 5-year-old sibling were hospitalized on the same day, and, although nuchal rigidity was absent in both, the CSF cell counts were 75 and 239, respectively, and ECHO 9 virus was recovered from their stools. In 46% of the patients the CSF cell count was 200 or more, and in only three patients was a cell count of 2000 to 2640 encountered. Cell counts in the range of 6000 to 8000 reported from Italy [14] and Switzerland [12] were not seen in the virologically proved cases in Milwaukee. The differential cell count varied considerably, from 15% to 98% polymorphonuclear cells in CSF obtained within 24 hours of presumable onset to less than 15% in those obtained later. The total protein also varied considerably, from normal to a maximum of 115 mg. %. The CSF sugar was in no instance less that 46 mg. %, and in only a few instances was it 70 mg. % or over, with a maximum of 98 mg. %.

The manner in which the clinical laboratory findings on the CSF may suggest another etiologic agent are illustrated by the following two patients, whose stools and CSF failed to yield a virus in monkey kidney tissue culture: 1. The CSF cell count was 1158, with 98% polymorphonuclear leukocytes within 24 hours after onset (which would not necessarily exclude ECHO 9), but the total protein was 340 mg. % (higher than any encountered in cases with ECHO 9) and Hemophilus influenzae was cultured from the CSF. 2. The CSF cell count was 4596, *predominantly polymorphonuclear leukocytes six days after onset of illness;* protein, 212 mg.; sugar, 39 mg., with a blood sugar of 230 mg. and chloride of 600 mg.; although bacteria were not seen in a smear of the CSF, satisfactory cultures were not available prior to antibiotic therapy; the blood leukocyte count was 26,500, with 88% polymorphonuclear cells; altogether this picture is more compatible with a diagnosis of bacterial meningitis, the only virus producing a similar picture in the CSF being that of lymphogranuloma venereum.[19]

A slight to moderate leukopenia, with a relative granulocytopenia, was found in the majority of the virologically proved cases; a few patients exhibited a slight leukocytosis, with a maximum cell count of 12,500. The blood sedimentation rate was increased in the majority of patients, an observation also recorded by others.[12,14] Slight microscopic hematuria occurred in nearly 50%, and low-grade proteinuria, in about 10% of the patients. These conditions were apparently transient and occurred only during the febrile phase of the illness.

Clinical Characteristics of Confirmed ECHO 9 Virus Disease in Patients Remaining at Home

Among the 114 members of the 22 households containing 1 or more persons from whom ECHO 9 virus was recovered, 77 persons (67%) had an acute febrile illness during August. The symptoms experienced by 48 persons whose stools yielded ECHO 9 virus are summarized in Table 8. It is evident, by comparison with the data in Table 6 on hospitalized patients, that in general the patients remaining at home experienced the same symptoms as those with the aseptic meningitis syndrome. The incidence of vomiting and abdominal pain was higher in the hospitalized group. Individual histories suggest that headache was generally severer in the hospitalized group. The incidence of neck and back pain was higher among hospitalized children under 10 years of age but about the same in both groups among older children and adults. The number of days on which fever was recognized varied from 1 to 18, with a median of 3, as compared with a median of 6 for the hospitalized group. Recrudescence of illness occurred only among 4 of the 48 persons, and in 1 of these a generalized rash occurred during both the initial and recrudescent episodes. It is highly probable that many persons with ECHO 9 virus disease who remained at home would have been found to have the aseptic meningitis syndrome if lumbar punctures had been done. It has been our experience both in Milwaukee and Cincinnati that objective signs of nuchal or spinal rigidity may be fleeting in many patients with ECHO 9 virus disease.

Characteristics of Rash in Confirmed ECHO 9 Virus Disease

A study of the rash in 43 persons with virologically confirmed ECHO 9 virus disease, in both hospital and home groups, indicated that generally the rash appeared first on the face or face and neck. Spread to other parts of the body frequently occurred within the next 6 to 12 hours. In 25% of the patients the rash was observed only on the face; in 11%, only on the face and neck; in 8%, only on the face, neck, and chest, in 56%, on the face, neck, trunk, and extremities. The rash is macular or maculopapular, with few exceptions discrete, 1 to 3 mm. in diameter, faint pink to deep pink

TABLE 8.—*Symptoms in Forty-Eight Persons with Acute Febrile Illness During August from Whose Stools ECHO 9 Virus Was Isolated (Twenty-Two Study-Group Families)*

	Age, Yr.									
	0-4		5-9		10-19		20 & Over		All Ages	
Symptoms	No.	%	No.	%	No.	%	No.	%	No.	%
Fever	26	100	8	100	4	100	10	100	48	100
Headache	16	62	8	100	4	100	10	100	38	79
Vomiting	10	39	1	12	1	25	1	10	13	27
Sore throat	11	42	4	50	2	50	4	40	21	44
Pain in neck	6	22	2	25	3	75	7	70	18	37
Pain in back	2	8	3	37	2	50	4	50	11	23
Abdominal pain	3	12	0	0	0	0	0	0	3	6

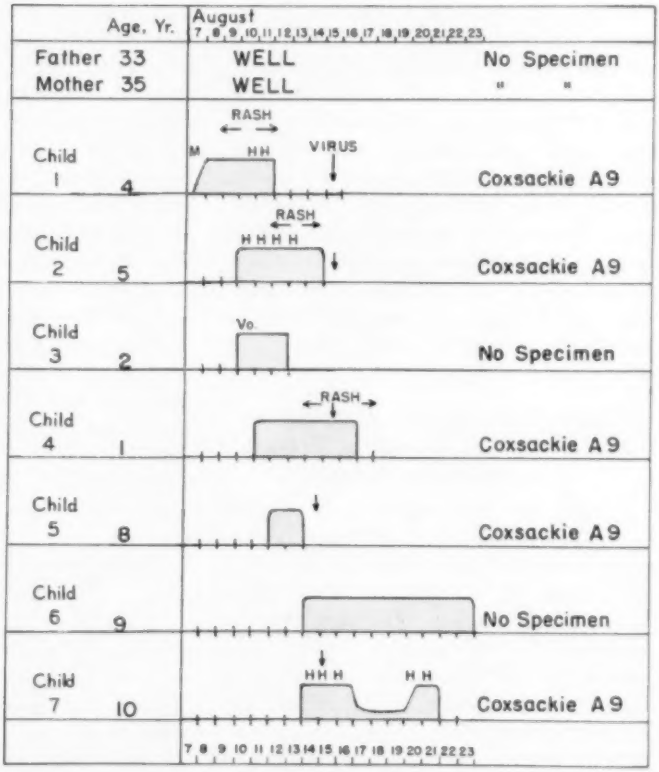

Fig. 3.—Coxsackie A 9 febrile illnesses, some with rash, in one family. Shaded areas indicate periods of fever; *H*, headache, *M*, malaise, *Vo.*, vomiting. Days of August, 1957, are given at top and bottom.

in the beginning, becoming pinkish-tan with the passage of time. It does not itch or desquamate. The rash, as a rule, appears during the course of the febrile period and persists for a day or less in some patients and for as long as nine days in others, the median being four to five days. A petechial rash was seen in only one virologically proved case in Milwaukee, but a diffuse petechial rash, resembling that in meningococcemia, was observed in three patients during the 1956 Canadian outbreak,[18] although it was not stated that infection with ECHO 9 virus was specifically established in these three patients.

Precise observations on the incidence of enanthem are not available, but yellowish or grayish-white spots, 1 to 3 mm. in diameter, were seen on the buccal mucosa or tonsillar fauces, or both, of some of the patients.

Febrile Illnesses with Rash Associated with Other Enteroviruses During Summer of 1957 in Milwaukee

The only enteroviruses, aside from ECHO 9, that have previously been associated with febrile illnesses with rash are ECHO 4 virus[10] and ECHO 16 virus.[1,20] While ECHO 9 virus played the dominant role in Milwaukee in 1957, at least four other enteroviruses were recovered from cases of febrile illnesses with rash: Coxsackie A 9, ECHO 2, ECHO 14, and ECHO 16.

Coxsackie A 9 virus was recovered from the stools of five children of a family consisting of two adults and seven children (Fig. 3). All seven children had a febrile illness with onsets between Aug. 7 and 14, and three of them, aged 1, 4, and 5 years, with generalized rash and two others without rash yielded Coxsackie A 9 virus. The

rash was maculopapular in two and petechial in one and was present over the entire body in all three. The oldest child, aged 10, with the biphasic temperature curve, complained of neck and back pain and may have had aseptic meningitis. We have been informed by Dr. Dorothy Horstmann, of the Yale Poliomyelitis Laboratory, that during the summer of 1957 Coxsackie A 9 virus was isolated in Connecticut from several families with multiple cases of fever and rash; Dr. Robert Huebner, of the National Institutes of Health, also informed us that he had found Coxsackie A 9 in association with fever and rash in Bethesda, Md., several years ago. Kilbourne and Goldfield [19a] isolated Coxsackie A 9 virus from the stools of a 17-year-old girl who had a febrile illness with rash and severe, though transitory, encephalitis in whom the diagnosis was "postrubella encephalitis."

ECHO 16 virus was recovered from the stools of two children, aged 3 and 6 years, in one family. The parents were not ill and did not submit stools; there were no other children. The 6-year-old child became ill on July 28 with fever that persisted until Aug. 5; the symptoms during this period were headache, sore throat, and vomiting. After the child had felt better for about five days, the fever recurred, on Aug. 10, and upon physical examination, on Aug. 14, four lesions measuring about 2 mm. in diameter and multiple minute lesions, all dark red, were seen on the posterior palate. There was no rash, and the only other finding was palpable anterior cervical lymph nodes. The 3-year-old child became ill on Aug. 12 with fever that, according to the mother, persisted until Aug. 24. Headache, sore throat, and vomiting were present at different times during the illness. On Aug. 14 a physician noted the presence of a temperature of 100.4 F, conjunctivitis, and enlargement of the anterior cervical lymph nodes. A blotchy rash appeared on the face and arms on Aug. 16 and persisted until Aug. 18. The two patients with aseptic meningitis from whom ECHO 16 virus was recovered did not have a rash.

The ECHO 2 virus was recoverd from a 2-month-old baby with an aseptic meningitis syndrome; a macular erythematous rash was observed on the chest and soles of the feet 24 hours after onset of fever and persisted for 4 days. This child developed antibody for ECHO 2 virus but not for ECHO 9 virus. The ECHO 14 virus came from a 3-year-old child with an aseptic meningitis syndrome; the rash, described as scarlatiniform, was present on the abdomen and legs.

Fatal Suspect Cases of Encephalitis Encountered in Milwaukee During Summer of 1957

In pursuing our attempt to elucidate the role of ECHO 9 virus as a possible cause of severe or fatal disease of the nervous system, all suspect cases of severe encephalitis that came to our attention during the course of the epidemic were investigated. Although ECHO 9 virus was not associated with any fatal case, it may be worth while briefly to record the findings in the only three cases that came up for investigation.§

CASE 1.—A 5-month-old baby died on Oct. 3 at the Milwaukee Children's Hospital after an illness of six days' duration characterized by fever, repeated vomiting of bloody or coffee-ground material, slight enlargement of the liver, and coma of four days' duration. There were only 4 cells and 15 mg. % of protein in the CSF, and the blood leukocyte count was 27,200, with 61% neutrophils. An x-ray examination of the chest was negative, and the urine was essentially normal. ECHO 18 virus was recovered from the stool, and the serum contained no antibody, indicating that this was an acute infection. ECHO 18 virus [17] has been clearly associated with diarrheal disease of early infancy,[18] but this is the first instance of its isolation from a fatal case. There was no necropsy, and while one cannot be certain that the ECHO 18 virus was responsible for the fatal disease in this child it is at least suspect and will bear further watching. It is noteworthy that an older sibling of this baby, one week earlier, had a febrile illness, and a neurtralization test on her serum obtained two months later revealed antibodies for ECHO 18 virus.

CASE 2.—An 8-month-old baby died on Sept. 4 at the Johnston Municipal Hospital after an illness of five days' duration characterized by

§ The histories and observations on Cases 1 and 3 were supplied by Dr. J. C. Peterson.

fever, moderate diarrhea, convulsions, and marked nuchal and spinal rigidity with frequent bouts of opisthotonus. The CSF was bloody and contained only 5 lymphocytes. The urine had large amounts of albumin and very many erythrocytes. The blood leukocyte count was 20,800, with 80% neutrophils. At postmortem examination the brain showed no evidence of inflammatory or neuronal disease but was full of calcium deposits such as are seen in hypoparathyroid disease. The kidneys showed extensive fibrinoid deposits in the glomeruli, and the lungs exhibited an interstitial pneumonitis. No virus could be recovered in monkey kidney tissue cultures from the stools, small intestine, mesenteric lymph nodes, liver, medulla, or brain.

CASE 3.—A 7-month-old baby, was admitted to the Milwaukee Children's Hospital on July 27, where a diagnosis of acute encephalitis was made because of fever, convulsions, wandering eyes, coma, and progressive development of generalized rigidity, with a pleocytosis ranging from 133 to 30 cells, mostly lymphocytes, with normal CSF protein and sugar. The child died two months later. Neutralization tests on serial sera revealed no antibodies for either ECHO 9 or herpes simplex viruses.

Estimate of Incidence of ECHO 9 Virus Disease During 1957 Epidemic in Milwaukee

The ECHO 9 virus epidemic in 1957 in Milwaukee may be assumed to have covered predominantly the period between the latter part of June and the end of September (Fig. 1). The earliest specimens available for test were from two patients with onset on June 24, and both yielded ECHO 9 virus. The last patient from whom this virus was recovered had an onset on Sept. 22. There was a marked increase in respiratory disease at the end of September, much of it probably due to the Asian strain of influenza A virus.

Although the true incidence of ECHO 9 virus disease in Milwaukee cannot be calculated by proper statistical methodology, the available data, nevertheless, permit a crude and probably conservative estimate. As was previously described, public health nurses visited 2447 households containing 11,403 persons (average 4.7 per household) during the peak of the epidemic, between Aug. 14 and Aug. 20, and found 62 households in which one or more persons had an acute febrile illness associated with signs and symptoms considered to be compatible with ECHO 9 virus disease. Physicians checked on 53 households and, with one exception (a family with typical measles in which no ECHO 9 virus was found in the patients or associates), confirmed the nurses' findings. The virologic studies on 27 of these families (including the 1 with measles just mentioned) indicated that ECHO 9 virus was active (58 strains recovered) in 22 households containing 114 persons (average 5.2 per family). Although 55 persons were actually ill in these 22 families during the week of the nurses' visits, the statistical computation will be based only on the 39 persons whose illness began during the week ending Aug. 17, in order that a ratio may be established between them and the number of hospitalized Milwaukee residents whose illness began during the same week. Since the remaining 35 households with illness had an average family size of 5.1, we may assume that a proportionate number of their illnesses was probably caused by ECHO 9 virus during the week ending Aug. 17 ($39/27 = x/35$), i. e., 51 persons.

Accordingly it is assumed that 90 persons, with onset of ECHO 9 virus disease during the week ending Aug. 17, resided in 2447 households containing 11,403 people in the City of Milwaukee proper. This represents 1 case of ECHO 9 virus disease, with onset during that week, for every 126.7 persons residing in households containing a comparable number of people with comparable age distribution. Census data indicate that about 375,000 of Milwaukee's 740,000 inhabitants are members of households whose family size and age distribution closely approximate those of the 2447 households visited by the public health nurses. These figures (375,000/126.7) suggest that 2960 cases of ECHO 9 virus disease, with onset during the week ending Aug. 17, may have occurred in the families with an average of three children, comprising about 50% of the city's population. Many of the hospitalized pa-

tients with proved ECHO 9 virus disease came from families with a size and age distribution different from those used in the above estimate, but we have no data which can be used to estimate the incidence of the disease in the remaining 365,000 inhabitants of Milwaukee. If we assume that the incidence of the disease was approximately half in this latter group, a crude estimate would be that 4400 persons in the city proper probably had ECHO 9 virus disease with onset during the week ending Aug. 17.

The number of hospitalized Milwaukee residents with aseptic meningitis having an onset during the week ending Aug. 17 was 23. Since laboratory studies indicated that ECHO 9 virus was the etiologic agent in approximately 90% of the hospitalized patients, it may be assumed that 21 of the 23 cases were caused by this virus. If there were at least 4400 unhospitalized cases of ECHO 9 virus disease during a week in which 21 persons were hospitalized with aseptic meningitis, the ratio between the former and the latter is 210:1.

For a variety of reasons it is highly improbable that a consistent ratio between unhospitalized and hospitalized cases of ECHO 9 virus disease prevailed in Milwaukee during the entire epidemic period. There are many indications that hospitalization greatly diminished after Aug. 17, when it became widely known that ECHO 9 virus, rather than the polioviruses, was the predominant cause of the aseptic meningitis seen by physicians. However, if such consistency is assumed to exist, the incidence of the disease during the four-month period in the city proper may be estimated as follows: Ninety per cent of the 149 cases of hospitalized patients, or a total of 134, may be assumed to have been caused by ECHO 9 virus; if there were 210 cases of the disease at home for each case in the hospital, the total number was 28,140.

If one includes the environs of Milwaukee, the total number of patients in Milwaukee hospitals during this period was 213. Applying the same formula, the estimate for Milwaukee and environs becomes 40,320 probable cases of ECHO 9 virus disease.

On the basis of this estimate it would appear that the total morbidity of ECHO 9 virus disease during this epidemic was only about 4%. Since the family studies, described earlier, indicated that about 85% of the infections were associated with clinical disease and also that most of the children under 15 years of age were susceptible, it was of interest to obtain an estimate of the extent of immunity to this virus in Milwaukee prior to the 1957 epidemic. It was possible to obtain frozen serum specimens from 30 pregnant women, 16 to 43 years of age, who had been bled between August, 1956, and May, 1957, prior to the 1957 epidemic.‖ These sera were tested ¶ for antibody against both the prototype, "Hill" strain as well as one of the antigenically different Milwaukee strains of ECHO 9 virus, but the results were essentially the same with the two strains. The data shown in Table 9 indicate that 57% had no antibodies for ECHO 9 virus; all the positive samples were from women 25 years of age or older. Further serologic studies on pregnant women at the end of the 1957 epidemic in Milwaukee (carried out on specimens obtained from Drs. J. C. Peterson and L. B. Glicklich) indicate a marked difference between those who had a history of "compatible" illness during the epidemic and those who were not ill (Table 9). The fact that 79% of the pregnant women without history of illness had no antibodies for ECHO 9 virus at the end of the epidemic suggests that the true incidence of susceptibles among the older age groups prior to the epidemic was probably somewhere between 57% and 79%.

The data presented in Table 10 give some idea of the incidence of infection in susceptible mothers with at least three or more

‖ These specimens were made available by Drs. T. J. Greenwalt and N. G. Maxwell, of the Milwaukee Blood Center.

¶ Dr. S. Wang helped in the testing of the sera.

TABLE 9.—*Incidence of Antibody for Milwaukee Strain of ECHO 9 Virus Among Pregnant Women in Milwaukee Before and at End of 1957 Epidemic*

Date Bled	Group	No. Tested	Per Cent with Antibody in Indicated Category		
			1:10+	Undiluted Serum Only	None
Before epidemic (8/56-5/57)	Women with Rh antibodies	30	20	23	57
End of epidemic (Late 9/57)	No illness	28	7	14	79
	Compatible illness	28	57	7	36

pre-school-age children, although the numbers are obviously too small for statistical evaluation. From Dr. Greenwalt, of the Milwaukee Blood Center, it was possible to obtain blood specimens and histories from nine of the women whose blood specimens were available prior to the epidemic. It may be noted that, with one exception (Mother 4), in which the blood was taken only two days after onset of illness in a child, the occurrence of acute febrile illnesses in the mothers or their children was associated with appearance of antibody for ECHO 9 virus.

The high incidence of negative tests for ECHO 9 antibody in pregnant women without history of illness bled at the end of the epidemic (Table 9), as well as in others in the same category bled late in 1957 and early 1958, indicates that the estimated morbidity rate of approximately 4% is probably in the correct range and that only a fraction of all the susceptibles were infected during the course of the 1957 epidemic in Milwaukee. This is understandable in the light of the studies on Milwaukee families with and without illness, which indicated that the virus was spread predominantly by small children and was largely limited to households with compatible illnesses.

Incubation Period

The incubation period, defined as the interval between acquisition of virus and the appearance of clinical manifestations, could not be delineated from our data on the 22 families with ECHO 9 virus disease, because there was no way of knowing just when the virus was acquired within the family or from a common source outside the family. There were only two instances in which virus was recovered in a familial associate before onset of illness: In one it was 5 days and in the other 20 days prior to onset of a compatible illness. While it is thus possible that the incubation period may be as long as 5 or 20 days, one cannot be certain because these persons were not again tested at the time of their illness to exclude another etiologic agent. In four other family associates compatible illnesses developed 2, 9, 12, and 12 days, respectively, after a stool without detectable virus had been passed.

TABLE 10.—*Observations on Nine Milwaukee Families in Which Mothers Had No ECHO 9 Antibody Prior to Epidemic*

Mother	Age, Yr.	ECHO 9 Antibody in Mother		Children		Illness During Epidemic	
		Before Epidemic	End of Epidemic	No.	Ages, Yr.	Mother	Children
1	25	0	20	3	9/12, 3, 4	July: fever, stiff neck	One on Sept. 1, fever and rash
2	27	0	>20	4	7/12, 3, 4, 6	Aug.: 104 F, stiff neck	3 in August before mother
3	32	0	>20	4	4/12, 3, 8, 9	None	2 on 9/25/57 and 10/1/57; mother bled 10/8/57
4	24	0	0	5	9/12, 2, 4, 5, 6	None	1 on 9/30/57; mother bled 10/2/57
5	36	0	0	4	2, 5, 8, 9	None	None
6	26	0	0	2	7/12, 19/12	None	None
7	33	0	0	2	7/12, 6	None	None
8	41	0	0	2	8/12, 15	None	None
9	22	0	0	0	--	None	--

Behavior and Properties of Milwaukee Strains of ECHO 9 Virus

Quantitative studies on multiplication of ECHO 9 virus in various sites of the body, the duration of virus excretion, the antigenic characteristics of the virus, the nature of the antibody response, and the pathogenicity of the viruses for newborn mice were carried out, and the results obtained with material from Milwaukee and Cincinnati will be published in detail elsewhere.[21,22] The pertinent information required for a better understanding of the natural history and epidemiology of the disease may be summarized as follows.

Site of Virus Multiplication.—Virus was recovered with greatest ease from the posterior pharyngeal wall, the stools, and the cerbrospinal fluid. No virus was found in any of the acute-phase serum specimens obtained in Milwaukee, but studies on sera obtained in Cincinnati indicated that viremia occurs prior to onset of clinical manifestations and virus is only rarely demonstrable in the serum obtained within 24 hours after onset. No virus was found in swabs from the nasal mucosa of patients at a time when it was present in the posterior pharyngeal wall. The virus probably does not multiply in the buccal mucosa, gums, or anterior portion of the tongue, because it was recovered only once from mouth swabs in low concentration (32 TCD_{50} per swab) at a time when the swabs from the posterior pharyngeal wall yielded 125,000 TCD_{50} of virus. The concentration of virus in the stools, even during the first few days after onset of illness, was usually in the range of only 50 to 500 TCD_{50} per gram, and unless minimal amounts suffice for human infection it is difficult to account for the high intrafamilial contagiousness of the virus. The larger amounts, in the range of 1000 to 10,000 TCD_{50} per gram, were excreted by children under 4 years of age oftener than by older children or adults, which is in line with the epidemiologic indications that children under 6 years of age oftenest bring the virus into the family. The amount of virus in the cerebrospinal fluid varied from only a few TCD_{50} to a peak of 60,000 TCD_{50} per milliliter.

Duration of Virus Excretion.—Tests on 152 stool specimens obtained at different times after onset of illness in hospitalized and unhospitalized persons in Milwaukee with proved ECHO 9 virus infections indicated the following: 86% positive during first week, 74% positive during second week, 37% positive during third and fourth weeks, and only 1 of 22 persons (5%), who excreted virus earlier, had a positive stool between 5 and 8 weeks—the one positive specimen was at 53 days. It should be noted that after the end of the second week the positive stools contained only traces of virus.

Antigenic Characteristics of the Virus.—It was mentioned earlier that some difficulty was encountered in the identification of most of the Milwaukee strains because the prototype ECHO 9 antiserum did not neutralize these strains as well (i. e., to as high titer or as many infective doses) as it did the homologous, prototype "Hill" strain. However, Milwaukee patients who developed neutralizing antibody for the Milwaukee strains invariably did so also for the prototype "Hill" strain. Evidence indicating that the Milwaukee strains were not inherently more difficult to neutralize was found in the fact that the human convalescent sera usually gave higher titers against similar doses of the Milwaukee strains than against the "Hill" strain. These data taken together with the tests (mentioned earlier) on adult sera from Milwaukee residents bled prior to the epidemic indicate that the Milwaukee ECHO 9 viruses were antigenically only slightly different from the prototype—a finding that is not uncommon with different strains of other ECHO viruses.[1]

Nature of Antibody Response.—Tests for neutralizing antibody on the acute- and convalescent-phase sera of 22 Milwaukee patients indicated that this antibody appears very early after infection and can be present within 24 hours after onset of symptoms.

When doses in excess of 100 TCD_{50} were used in tests with early convalescent sera, high titers obtained in readings on the second to the fourth days frequently were very low or negative on the final reading at eight days. This phenomenon, probably associated with antibody of low avidity, will be described in greater detail elsewhere.[21] We did not find the complement-fixing antigen prepared from monkey tissue cultures entirely satisfactory (low potency and partly anticomplementary), but the data obtained suggest that the complement-fixing antibody appears much later after infection than the neutralizing antibody and probably does not persist very long.

Pathogenicity of Milwaukee Strains for Newborn Mice.—Although the prototype "Hill" strain of ECHO 9 virus and seven other strains recovered earlier in this laboratory from healthy children were not pathogenic for newborn mice, even after several passages in tissue culture, a varying proportion of the strains recovered from the European epidemics[5,6,10,11,14] proved to be pathogenic, but only after passage in tissue culture. A total of 35 original specimens (26 stools, 9 CSF) from Milwaukee patients shown to contain ECHO 9 virus were injected into newborn mice, and no paralysis was observed, except with 1 stool extract which in addition to the ECHO 9 virus also contained a noncytopathogenic Coxsackie A virus. After a single passage in tissue culture, all but five of the Milwaukee strains proved to be paralytogenic in mice, with the production of muscle lesions—a result comparable to those obtained with the European strains. Quantitative studies to be published in detail elsewhere[22] indicated that naturally occurring ECHO 9 viruses possess a varying and limited capacity for multiplication in the muscles of newborn mice, an inoculum of more than 10^5 TCD_{50} usually being required for the production of paralysis, and that consecutive passages in mice favor the selection of virus particles with increasing pathogenicity for newborn mice. Although this has raised a question of classification, it is obvious that some of the properties that are the predominant characteristic of one group of viruses in the family of enteroviruses, e. g., the effect of polioviruses on primate neurons, may be shared to a limited degree by certain strains of another group, e. g., the limited neurotropism for primate neurons of Coxsackie A 7 and A 14 and of some of the ECHO viruses.[1] On this basis, there are no valid reasons for reclassification of the ECHO 9 virus.

Comment

The virologically controlled clinical and epidemiologic studies on the epidemic of ECHO 9 virus disease during the summer of 1957 in Milwaukee have provided the following new information.

1. Approximately 85% of the infections with this virus resulted in clinically recognized illness.

2. The infection was almost entirely limited to households with illness and was spread predominantly by young children to one another and to almost all the nonimmune members of the household.

3. The amount of illness caused during the months of June to September by the extensive spread of this virus can be very large. The virologically controlled survey of 2447 families containing 11,403 persons in Milwaukee permitted a crude and probably conservative estimate of 28,140 cases of illness in the city proper (population 740,000) and about 40,000 in the city and environs.

4. Tests on stored serum specimens obtained prior to the epidemic indicated that ECHO 9 virus was not new to Milwaukee, since approximately 40% in the age group of 20 to 40 years had antibody for the epidemic strains. With a total estimated morbidity rate of approximately 4%, only a fraction of the total susceptible population was affected, as was evident in the high incidence of persons without ECHO 9 antibody among pregnant women who had no history of illness during the course of the epidemic and were bled subsequently.

5. The spectrum of clinical manifestations defined only on the basis of virologically proved cases in the homes as well as in the hospitals indicated that distinct signs of involvement of the central nervous system were rare. It was estimated that 210 persons were ill at home for every patient admitted to the hospital with signs of meningeal irritation or more extensive involvement of the nervous system. In many instances the signs of nuchal and spinal rigidity were so transitory that it is highly probable that many of the patients who remained at home also had aseptic meningitis. Signs indicative of more extensive involvement of the nervous system were extremely rare and in all instances transitory: in five patients the signs suggested involvement of the medulla with special reference to the vestibular nuclei, and in only one patient was there transitory paralysis, affecting chiefly the hip muscles. There were no fatalities.

6. The rash, as a rule macular or maculopapular and only rarely petechial, occurred in almost all children under 3 years of age and with diminishing frequency in older children and adults—about 44% in the 5- to 15-year group, and only 6% in those over 15 years of age.

7. During the course of this epidemic four other enteroviruses, playing a minor role, were found to be associated with febrile illnesses with rash—Coxsackie A 9 and ECHO Types 2, 14, and 16.

One of the most important consequences of infection with ECHO 9 virus requiring further study is its effect on the fetus, particularly during the early months of pregnancy. The high incidence of susceptibles among women of child-bearing age and their greater frequency and intimacy of contact with young children provide special opportunities for infection. One needs to consider both spontaneous abortion and congenital defects as possible consequences of infection not only with ECHO 9 virus but with the many other ECHO and Coxsackie viruses that can produce viremia and are so highly prevalent during the summer months. A controlled study of this problem among women who were pregnant during the 1957 epidemic in Milwaukee is now in progress in cooperation with Drs. Peterson and Glicklich, of the Milwaukee Children's Hospital.

Summary

During the summer of 1957 more than 200 patients were admitted to Milwaukee Hospitals for the most part with a tentative diagnosis of nonparalytic poliomyelitis. Some of the patients had rash. Among 101 patients whose stools or cerebrospinal fluid, or both, yielded viruses in monkey kidney tissue cultures, 90 were infected with ECHO Type 9 virus, 5 with other ECHO viruses (Types 2, 14, 16, and 18), 5 with Coxsackie viruses (A 9, B 3, B 4, and B 5), and only 1 with poliovirus (Type 3). A clinical and epidemiologic survey of 2447 families containing 11,403 persons, checked by a virologic study of 27 families with acute febrile illnesses and 25 without, led to an estimate of approximately 210 persons with ECHO 9 virus disease at home for each 1 in the hospitals. ECHO 9 virus infections were almost entirely limited to families with illness, and adults as well as children were affected. The total number of persons estimated to have been ill with ECHO 9 virus disease during the epidemic period was 40,000 for Milwaukee and environs and 28,000 for the city proper, with a population of 740,000.

Approximately 85% of ECHO 9 virus infections resulted in disease. The aseptic meningitis syndrome was often associated with only fleeting nuchal and spinal rigidity, and it is probable that many of the unhospitalized patients with pain in the neck and back may also have had involvement of the nervous system. Transitory signs of more extensive involvement of the nervous system were seen in only six patients; in five the signs suggested involvement of various regions of the medulla, and only one exhibited transitory

paralysis, chiefly of the hip muscles. There were no fatalities. The rash, macular or maculopapular and only rarely petechial, was commonest in the youngest children and least common in older children and adults—77% under 5 years of age, 44% 5 to 15 years of age, and only 6% over 15 years of age. An enanthem on the buccal mucosa and tonsillar fauces was also present in some patients. Coxsackie A 9 and ECHO Types 2, 14, and 16 were the only viruses recovered from a small number of patients who had febrile illnesses with rash, and it is evident that they were playing a minor role while ECHO 9 virus was playing the major role.

Antibody tests on sera obtained before and after the epidemic indicated that approximately 60% to 70% of the adult population had no previous contact with ECHO 9 virus and that only a small fraction of the total population had been infected by the time the epidemic had waned. One of the most important possible consequences of infection with ECHO 9 virus, or other similar viruses, requiring intensive study in the future, has to do with their potential role in spontaneous abortions and congenital defects.

Children's Hospital (29).

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Correspondence

AMERICAN HEART ASSOCIATION, INC.

To the Editor:—Knowing that doctors, of all people, demand for themselves and champion for others the right of fair and equal opportunity and the privilege of individual enterprise, I am addressing myself to the members of my own profession in the hope that they will help us to maintain the Heart Association as a free American institution.

During the past ten years, spearheaded by the work of the Association, great progress has been made in prevention and treatment of rheumatic fever and in development of new techniques to correct congenital and rheumatic abnormalities of the heart. We are now beginning to glimpse where and how the answers to strokes, coronary disease, and hypertension may be found.

However, as the American Heart Association begins its second decade as a national voluntary health agency, we find its continued success being threatened by a movement that is serious in nature and wide in scope. I refer to the organized effort being made to regiment the Association and all other health or welfare agencies into a single, united plan of fund raising.

During its early years the Heart Association participated on an experimental basis in more than 450 united funds. Today it has withdrawn from all but 270 of these funds. In ten years of experience with united funds we learned that a local heart association not only fails to raise as much money through a united fund as it does by its own independent campaign; it also tends to lose its identity, its sense of dedication and urgency, and its zeal in carrying out its independent program. In a word, it becomes dominated by the united fund. Therefore, the Heart Association, by an overwhelming vote of its democratically elected delegates representing all parts of the country, has decided not to participate any further in united funds.

However, through our previous experience with united funds we became well acquainted with their tactics. What usually happens in a community is that a small body of citizens, usually local business executives, self-motivated or persuaded by united fund organizers, become annoyed by "so many drives" and decide to reduce the number of these drives. Invariably they come to the conclusion that volunteers and givers are in revolt against so many drives, and that the easy answer is "one campaign for all." They decide to have only a single fund and to distribute the proceeds according to their ideas of local needs, not according to donors' wishes or to national needs for health programs.

Almost immediately they begin to run into difficulties. Heart, cancer, polio, and other associations decline to participate because of established policies designed to protect donors' wishes and to separate national research agencies from local charities. This frustrates the united fund promoters, who begin to attack some of the very causes they started out to support. As one point of their attack, they focus on physicians and on local medical societies in an effort to induce them to endorse the united fund and thus to force the health agencies into line. They use many devices, including personal influence, organizational pressure, or even threats.

In the face of such tactics the national voluntary health agencies have been hard pressed to protect themselves. They have not wished to launch a counterattack. They do *not* want to fight united funds, but merely to remain independent of them.

Whether we like it or not, the medical profession is directly involved in this controversy. Medicine cannot continue to ignore or condone the threats to itself through the increasing attacks by united funds on the voluntary health agencies. For united funds are promoting a movement under which uninformed, though conceivably well-intentioned, local laymen are entering directly into national medical fields of health and disease and deciding where and when funds should be spent for each purpose and how much.

The united fund philosophy of a single plan of fund raising and fund spending (controlled of course by united fund) if extended logically could apply to the establishment of a single type of medical care or a single plan of health insurance.

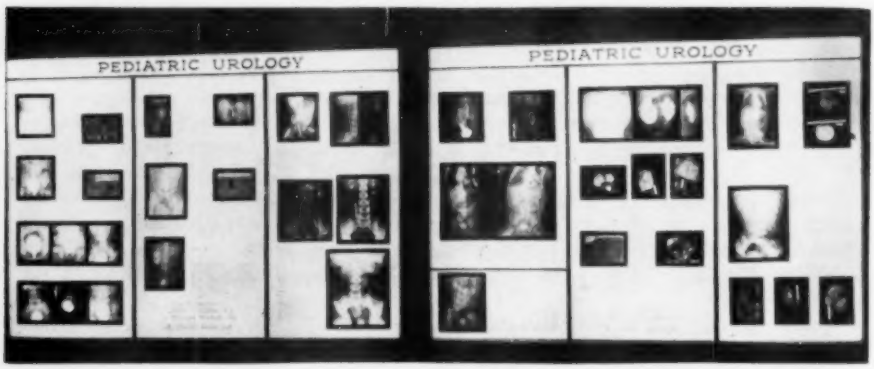
Therefore, every physician should give most thoughtful consideration to the problems created by the united fund philosophy and tactics. Freedom is indivisible. It is for all, or for none. The medical profession will help to preserve its own freedom in the future if it insists now, through its county, state, and national organizations, that the ethical voluntary health agencies be freed of further coercion by united funds.

ROBERT W. WILKINS, M.D.
President
American Heart Association
44 E. 23d St., New York 10.

Scientific Exhibits

Pediatric Urology

SAM G. JAMESON, M.D.; JAMES O. COOPER, M.D., and J. SCHULER McKINNEY, M.D., El Dorado, Ark.



Numerous pediatric urological cases are presented in a brief but concise manner by x-rays, color transparencies, and legends. Cases presented exemplify congenital anomalies, obstructive uropathy, infection, tumor, and trauma. This exhibit is especially valuable for the generalists and the pediatricians, as the indication for urological investigation is indicated in each case.

Many urological symptoms are overlooked in children only to reappear later, in adult life, associated with irreparable damage to part or all of the urinary tract. We believe that the relatively high incidence of pediatric urological pathology is frequently not generally realized, but proof of this high incidence is submitted by the fact that the following cases (with two exceptions), and numerous other cases not presented in this exhibit, were discovered in a four-year period in only three counties in Arkansas, with total population of only 130,000. The short history accompanying each case summarizes the presenting symptoms, physical findings, and/or urine findings indicating urological examination.

Recorded for publication Jan. 29, 1958.

This exhibit received the John H. Morrissey Award as the outstanding scientific exhibit in the Section on Urology at the 106th Annual Meeting of the American Medical Association, New York, June 3-7, 1957.

Abnormal Urinary Symptoms

CASE 1.—A 7-year-old girl had recurrent pyuria, frequency, and enuresis in spite of antibiotics and chemotherapy. Urological examination revealed bladder neck obstruction, for which transurethral resection was done.

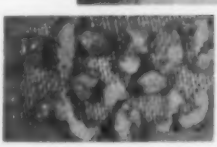


Fig. 2 (Case 1).—Retrograde cystogram showing bladder dilatation without influx.

Fig. 3 (Case 1).—Tissue removed from bladder neck.

CASE 2.—A 2½-year-old girl had chronic pyuria, diurnal enuresis, and nocturnal enuresis in spite of antibiotics and chemotherapy. Urological examination revealed bladder neck contracture, for which transurethral resection was done.

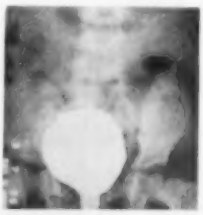


Fig. 4 (Case 2).—Retrograde cystogram showing trabeculation with slight left ureteral reflux.

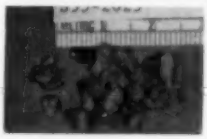


Fig. 5 (Case 2).—Tissue from bladder neck.

Figures 6 through 11 show retrograde cytograms in other children with similar symptoms who were found to have bladder neck or urethral obstruction.

Fig. 6 (Case 3).—An 11-year-old girl with bladder trabeculation. No reflux.

Fig. 7 (Case 4).—An 8-year-old boy with bladder dilatation. No reflux.

Fig. 8 (Case 5).—A 3-year-old girl with bilateral reflux.

Fig. 9 (Case 6).—A 2½-year-old girl with bilateral reflux.

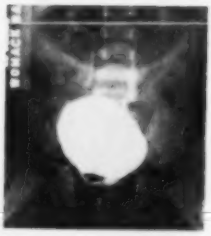


Fig. 10 (Case 7).—A 3-month-old girl with left reflux.

Fig. 11 (Case 8).—A 6-year-old girl with left reflux.

CASE 9.—A 14-year-old boy had a long-standing history of straining to void, pyuria, and marked generalized underdevelopment. Autopsy revealed irreparable damage of the left kidney and ureter, secondary to bladder neck contracture and marked hypertrophy of the interureteric ridge. Right kidney was hypoplastic.

Figure 12 (Case 9)

CASE 10.—A 5-year-old girl had straining to void, getting clothes wet after voiding, and nocturnal enuresis. External genitalia revealed fusion of labia, which caused incomplete emptying of bladder, with portion of voided urine being left in vagina until she stood erect after voiding. Permanent separation of labia was performed.

Figure 13 (Case 10)

CASE 11.—A 7-year-old girl complained that her underclothes stayed slightly damp at all times, even immediately after voiding. Urological examination revealed right ureteral orifice ectopically opening into vagina. Right nephrectomy was performed, which revealed hypoplastic kidney.

Fig. 14 (Case 11).—Intravenous pyelogram, showing normal left kidney. Right kidney was hypoplastic and nonfunctioning.

Fig. 15 (Case 11).—Hypoplastic kidney.

CASE 12.—An 8-month-old boy had complete anuria following an episode of diarrhea. Urological examination revealed congenital absence of left kidney and ureter, with right kidney and ureter blocked by uric acid crystals (precipitated secondary to dehydration and acidosis during diarrhea). After the crystals were dissolved with irrigations of sodium bicarbonate and intravenous sodium lactate, further examination revealed congenital stricture of ureteropelvic junction with resulting hydronephrosis, for which ureterocalyceal anastomosis was performed.

Figure 16 (Case 12)

CASE 13.—A 3-year-old boy had recurrent abdominal pain, albuminuria, and microscopic hematuria. He was found to have stricture of terminal ureter, bilateral, for which bilateral ureteral reimplantation was done.

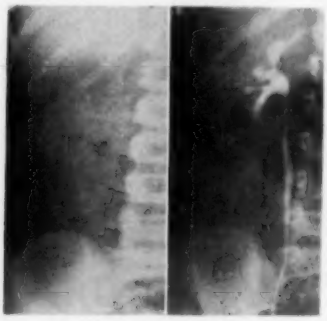
Figure 17 (Case 13)

CASE 14.—A 2-month-old girl had pyuria and fever. Several retrograde pyelograms revealed consistent abnormality of course of right ureter with incomplete filling of pelvis and calyces. Surgical exploration revealed ureter to be compressed and displaced upward by thick, wide band of fibrous tissue, which when divided immediately allowed ureter to assume normal position and course without compression.

Figure 18 (Case 14)

CASE 15.—A 5-year-old girl with persistent pyuria was found to have a stone in the calyceal diverticulum. Urine culture with sensitivity tests was done, after which the child was given a specific antibiotic for several weeks. Following this treatment, urine culture became negative and the patient became asymptomatic.

Figure 19 (Case 15)



CASE 16.—A 10-year-old boy had mild persistent pyuria and nocturnal enuresis. Urological examination revealed horseshoe kidney with minimal delayed drainage. Specific antibiotic therapy resulted in negative urine culture and cure of enuresis (the latter was due to bladder irritation resulting from infection).

Figure 20 (Case 16)

CASE 17.—A 7-year-old girl had recurrent pyuria, chills, fever, and left flank pain. She was found to have compression deformity of the collecting system of the left kidney. Surgical exploration revealed cortical abscess of the left kidney.

Figure 21 (Case 17)

CASE 18.—A 14-year-old boy had chronic pyuria, frequency, nocturia, and dysuria. Intravenous pyelogram revealed changes consistent with tuberculosis of left kidney, confirmed by smear and culture. He was given antituberculosis drugs for two months, after which nephroureterectomy was performed. The use of antituberculosis drugs was continued several months postoperatively.

Figure 22 (Case 18)

Non-Urinary-Tract Anomalies Associated with Urinary Tract Anomalies

CASE 1.—A 6-year-old girl had meningocele and spina bifida. Retrograde cystogram revealed neurogenic bladder.

Figure 23 (Case 1)

CASE 2.—A 13-month-old boy had cleft palate and glandular hypospadias. There were no urinary symptoms. Intravenous pyelography was done because of these two external abnormalities, revealing hydroureter and early hydronephrosis, secondary to congenital stricture of the ureterovesical junction.

Figure 24 (Case 2)

CASE 3.—An 11-month-old boy had partial to complete absence of the musculature of the left flank and abdominal wall, associated with other skeletal defects. There were no urinary symptoms. Urological examination was done because practically every person with abdominal wall defect has associated urinary tract abnormality. Examination revealed congenital absence of the left kidney and ureter, with dilated right ureter ectopically opening into the seminal vesicle. Surgical correction consisted of implantation of the right ureter into the bladder.

Figure 25 (Case 3)

Trauma

A 10-year-old boy had an abdominal mass and gross, total hematuria following a fall. Intravenous pyelography revealed medial deviation of the right ureter and kidney, secondary to retroperitoneal hematoma. The left kidney was congenitally malrotated. The child did well on a conservative regimen. Because congenital anomalies of the urinary tract are more susceptible to injury, every injury should be carefully investigated, not only to determine extent of injury but also to determine whether congenital anomalies are present.

Abdominal Masses

CASE 1.—A 21-month-old boy had a large mass palpable on each side of the abdomen, extending into each flank. Intravenous pyelography revealed bilateral giant hydronephrosis for which bilateral nephrostomy was performed. After stabilization of kidney function, left pyeloureteroplasty was performed. In spite of essentially satisfactory pyelographic result, the child developed bilateral pyelonephritis, which, with markedly decreased kidney function, caused his death.

Fig. 27 (Case 1).—Six-hour intravenous pyelogram.

Fig. 28 (Case 1).—Pyelogram before pyeloureteroplasty.

Fig. 29 (Case 1).—Left pyelogram after pyeloureteroplasty.

Figure 26

Fig. 30 (Case 1).—Autopsy specimen.

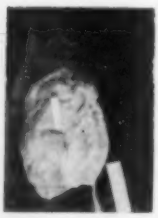


Fig. 31 (Case 1).—Autopsy specimen.

Fig. 32 (Case 1).—Autopsy specimen.

CASE 2.—A 10-day-old premature girl, weight 3 lb. 15 oz., had a left abdominal and flank mass. Intravenous pyelography and retrograde pyelogram were not diagnostic. Surgical exploration revealed left multicystic kidney with a normal right kidney. There was uneventful recovery after nephrectomy.

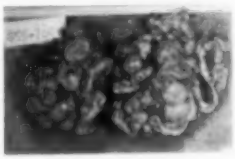


Figure 33 (Case 2)

CASE 3.—A 9-year-old boy had a large left flank and abdominal mass. Intravenous pyelography revealed a nonfunctioning left kidney. The right pyelogram was normal. Surgical exploration revealed left polycystic kidney, with right kidney grossly normal. There was uneventful recovery after nephrectomy.

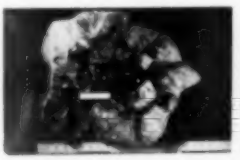


Figure 34 (Case 3)

CASE 4.—A 3-year-old boy had recurrent abdominal pain. Repeated urinalyses were negative. Careful palpation of the abdomen revealed a mass in the right upper quadrant found to be right hydronephrosis due to stricture of ureteropelvic junction. Surgical repair of the stricture was done.

Figure 35 (Case 4)

CASE 5.—Wilms' tumor. A 7-year-old girl had a huge abdominal and flank mass. Intravenous pyelography was not diagnostic. Retrograde pyelogram revealed compression deformity and caudad displacement of the right kidney. The left kidney was normal. Thoracoabdominal nephrectomy was begun, but, before the pleural cavity was opened, cardiac arrest developed. Cardiac massage restored heart activity for several minutes, but the patient died shortly thereafter. Autopsy revealed regional node involvement.

Fig. 36 (Case 5).—Wilms' tumor.

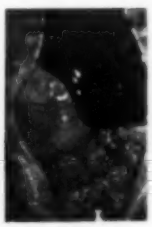


Fig. 37 (Case 5).—Autopsy specimen.

Fig. 38 (Case 5).—Autopsy specimen.

Fig. 39 (Case 5).—Autopsy specimen.

CASE 6.—Wilms' tumor. A newborn girl had a right flank and abdominal mass. Intravenous pyelography was not diagnostic. Retrograde pyelogram revealed compression deformity of the collecting system of the right kidney. The left kidney was normal. After nephrectomy was performed, at the age of 6 days, x-ray therapy was immediately begun. Surgical convalescence was satisfactory, but the irradiation caused progressive leukopenia, and the patient finally died at the age of 30 days, with a WBC count of 700. Autopsy revealed irradiation as the cause of death.

Fig. 40 (Case 6).—Wilms' tumor.

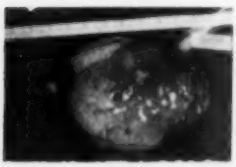


Fig. 41 (Case 6).—Wilms' tumor.

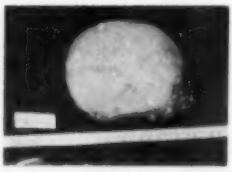


Fig. 42 (Case 6).—Wilms' tumor.

Summary

For the sake of brevity, only four basic indications for urological examination are outlined in this exhibit: (1) abnormal urinary symptoms, (2) non-urinary-tract anomalies, (3) trauma, and (4) abdominal masses.

There are several other indications for urological examination with less frequency of occurrence but unquestionably of as much importance as those listed. These indications, as well as more detailed information concerning pediatric urological disease, can be found in any one of several excellent textbooks on this subject.

Our singular purpose in presenting this exhibit is to further stimulate attention to and interest in pediatric urological problems, with the fervent hope that early recognition and correction of these problems will result in fewer and fewer adult urological cripples and urological deaths.

Jameson Urology Clinic, 700 W. Faulkner.

Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago

Abstracted by Philip N. Jones, M.D.

99, No. 6 (June) 1957

Infectious Diseases: Annual Review of Significant Publications.—This is the 22d annual review of infectious diseases and covers all significant publications during the year 1956 in this field. The author reviewed some 415 original articles and, in addition to abstracting the important material from these papers, has added his own comments and evaluations. This article obviously does not lend itself to abstracting but rather should be consulted in the original form by anyone interested in infectious diseases. The author's article is exceedingly comprehensive and yet is written in such a way that it is very readable.

American Heart Journal, St. Louis

Abstracted by Edward C. Matthews, M.D.

55, No. 3 (March) 1958

Congenital Mitral Stenosis Associated with Coarctation of Aorta, Bicuspid Aortic Valve, Hypoplasia of the Left Ventricle, Mitral Stenosis, Auricular Septal Defect, and Tricuspid Valvular Malformation. Colin A. Munroe, George E. Maha, and Edward S. Orgain.—p. 343.

Tetralogy of Fallot with Absent Left Pulmonary Artery: Report of a Case with Anomalous Development of the Right Hilar Vasculature and Nonfunctioning Right Lung. O'Neill Barrett Jr. and Weldon J. Walker.—p. 356.

Persistent Truncus Arteriosus: Report of a Case with Atypical Radiologic Features. Monty J. Goldberg and Maurice McGregor.—p. 360.

The Electrocardiogram in Interatrial Septal Defects and Its Correlation with Hemodynamics. Jorge Martins De Oliveira and Henry A. Zimmerman.—p. 369.

Tricuspid Atresia with Right Axis Deviation: Case Report and Review. John J. Sullivan Jr. and Joseph L. Mangiardi.—p. 450.

* Familial Pulmonary Stenosis and Deaf-Mutism: Clinical and Genetic Considerations. Sanford M. Lewis, Benjamin P. Sonnenblick, Lawrence Gilbert, and David Biber.—p. 458.

Unruptured Congenital Aortic Sinus Aneurysm With Aneurysmal Dilatation of the Aorta and Aortic Regurgitation Without Arachnodactyly. T. K. Lin, A. M. Diehl, J. W. Walker, T. N. Hall, D. C. Peete. —p. 463.

Familial Pulmonary Stenosis and Deaf-Mutism: Clinical and Genetic Considerations.—The occurrence of multiple cases of congenital pulmonary stenosis in a single family is uncommon. The authors report on a family in which the mother and three children had clinical pulmonary stenosis and two of the three children manifested coexisting deaf-mutism. In the mother and in two of the three affected children, the diagnosis of pulmonary stenosis was established by cardiac catheterization. In one child the diagnosis was based on clinical, electrocardiographic, and roentgen findings. Symptomatology was minimal in these patients, and in only one was a high right ventricular pressure demonstrated at catheterization.

The father and two other children had no evidence of congenital heart disease or deaf-mutism. The parents were not related, and family histories were negative for congenital defects. All five pregnancies had been uncomplicated.

The genesis of congenital cardiac lesions is generally difficult to define. Other authors have concluded that pulmonic stenosis has a larger genetic component than other congenital cardiac defects, and the concentration of congenital anomalies in this family points to a hereditary etiology. It is postulated that perhaps a dominant gene carried by the mother may have played a determinative role in the manifestation of the cardiac defect and that a recessive gene, carried by both parents, may have been responsible for the deaf-mutism. Accumulation of information in subsequent generations of this family may shed additional light on the hereditary factors involved.

* Infectious Diseases: Annual Review of Significant Publications. Robert A. Reimann.—p. 955.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

77, No. 2 (Feb.) 1958

The Chest Roentgenogram and Chest Roentgenographic Surveys Related to X-Ray Radiation Effects and Protection from Radiation Exposure. Executive Committee of the American Trudeau Society.—p. 203.

* Tuberculous Pleurisy with Effusion in Children: A Study of 202 Children with Particular Reference to Prognosis. Edith M. Lincoln, Pamela A. Davies, and Somchai Bovornkitti.—p. 271.

Filtration of Mycobacteria from Organic Solvents. Alfred J. Crowle.—p. 290.

The Effect of Thiocarbanidin and Related Compounds on Mycobacterium Tuberculosis var. Hominis in Vitro and in Vivo. Guy P. Youmans, Anne S. Youmans, and Leonard Douh.—p. 301.

Some Observations on the Composition of Bacterial Population of PAS-Resistant Mycobacterium Tuberculosis. M. Tsukamura.—p. 346.

Drug-Susceptibility Testing in Tuberculosis. F. P. Dunbar et al.—p. 350.

The Selective Activity of Fluid Thioglycollate Medium for Group Differentiation of Atypical Chromogenic Mycobacteria, Mycobacterium Tuberculosis, and Saprophytid Mycobacteria. M. L. Koch et al.—p. 356.

Childhood Miliary and Meningeal Tuberculosis in New York City. A. D. Chaves et al.—p. 359.

Isonicotinic Acid: Hypothesis of the Antituberculous Action of Isoniazid. E. Kruger-Thiemer.—p. 364.

Tuberculous Pleurisy with Effusion in Children: A Study of 202 Children with Particular Reference to Prognosis.—The poor prognosis of tuberculous pleurisy with effusion in adults has been stressed repeatedly, with development of systemic tuberculosis, mostly pulmonary, in from 25% to 65% of cases (Thompson, Sibley, Roper, and Waring).

The authors report 202 consecutive cases of pleurisy with effusion, presumably tuberculous, in children. In 176 of these the effusion was not associated with any form of tuberculosis with a serious prognosis, and among these children chronic pulmonary tuberculosis developed later in 5.7%. (In a group of 1000 consecutive cases of primary pulmonary tuberculosis of comparable age distribution under study in the same clinic, the later incidence of chronic pulmonary tuberculosis in the survivors has been 8.9%.) The incidence was nearly twice as high in the patients who were 10 years of age or older at onset of pleurisy. Extrapulmonary tuberculous complications developed in a further 3.4% of the group. Total mortality was 5.1%. Severe scoliosis developed in 4.5% of the group.

In the entire group of 202 patients, pleurisy with effusion was associated with generalized hematogenous tuberculosis. Mortality in this group was 65.4%, and it is probable that the pleurisy was not an important factor in creating this high rate.

This study confirms earlier statements to the effect that the presence of pleurisy with effusion in tuberculous infants does not appear to influence prognosis. The chief value of the study is presentation of evidence that while the prognosis of all children with tuberculous pleurisy with effusion is considerably less serious than that in adults, the difference, while still great, is considerably less striking in older children. As noted by the authors, this is probably due to the increased risk of developing chronic pulmonary tuberculosis as the child grows older.

Bulletin of the Johns Hopkins Hospital, Baltimore

Abstracted by Thomas K. Oliver Jr., M.D.

102, No. 1 (Jan.) 1958

* Fetal Blood Studies: VIII. Some Observations on the Transient Fetal Bradycardia Accompanying Uterine Contractions in the Human. Harry Prystowsky.—p. 1.

Aldolase Leak from Muscle of Mice with Hereditary Muscular Dystrophy. Kenneth L. Zierler.—p. 17.

A Genetic Study of a Defect in Glutathione Metabolism of the Erythrocyte. Barton Childs, William Zinkham, Eugene A. Browne, Exall L. Kimbro, and John V. Torbert.—p. 21.

Study of Two Abnormal Hemoglobins with Evidence of a New Genetic Locus for Hemoglobin Formation. Ernest W. Smith and John V. Torbert.—p. 38.

Studies on the Prophylaxis and Treatment of Tetanus: I. Studies Pertaining to Active and Passive Immunization. Sara Prudovsky and Thomas B. Turner.—p. 55.

* Studies on the Prophylaxis and Treatment of Tetanus: II. Studies Pertaining to Treatment. Thomas B. Turner, Emiliana A. Velasco-Joven, and Sara Prudovsky.—p. 71.

Fetal Blood Studies: VIII. Some Observations on the Transient Fetal Bradycardia Accompanying Uterine Contractions in the Human.—The cause of fetal bradycardia during labor is believed to be either fetal hypoxemia or decreased perfusion of the hindbrain of the fetus and resultant tissue hypoxia. The former theory has received widest recognition and the pathogenesis has been thought to be displacement of blood from the intervillous spaces and resultant hypoxia during uterine contractions because amniotic pressure exceeds intervillous

pressure. The author has clearly demonstrated that this theory is not correct. Blood taken from the intervillous spaces during uterine contraction and at rest reveals that blood can be readily obtained from the spaces during contraction. This would indicate that the uterine veins are occluded and that blood is trapped in the intervillous spaces. He further demonstrated that the mean pressure in the amniotic cavity and in the intervillous space is greater in the latter than in the former, both in the resting and in the contracting uterus, although only two studies were done in the same patient. Finally, 20 studies comparing oxygen gradient between the umbilical artery and vein with fetal heart rates were performed and no correlation could be observed. A fetal heart rate of 100 or below was observed among the group with a normal gradient, in those with a very low gradient, and in one of a series of six patients with a very high gradient when the mother was receiving oxygen. In the remaining 17 patients fetal heart rates were normal in all three groups.

When pressure was placed on the fetal skull (five cases) there was a reduction in fetal heart rate and in three the rate fell below 100, with a prompt rise to resting levels or above on release of pressure in all five subjects. The author concludes that the commonly observed slowing of fetal heart rate at the height of uterine contraction is related to increased intracranial pressure and resultant impaired medullary blood flow and not to hypoxemia.

In a small number of subjects the mean oxygen saturation (and calculated oxygen tension) of blood from the intervillous space was greater during uterine contraction than at rest. The range and overlap of the values is great; furthermore, no observations were made on the same patient. It seems very unlikely that oxygen content rises during the period of venous occlusion.

Studies on the Prophylaxis and Treatment of Tetanus: II. Studies Pertaining to Treatment.—Tetanus is a medical emergency and must be treated as such, because toxin appears in the serum as much as 36 hours before the appearance of symptoms. The immediate treatment consists of the *intravenous administration* of tetanus antitoxin in a single dose of 40,000 to 80,000 units. Except in the presence of horse serum sensitization, the dosage need not be repeated, because levels persist for at least one week. If sensitivity to horse serum occurs (manifested by the intradermal test) 1 ml. of epinephrine chloride 1:1000 is given intramuscularly 15 minutes before administration of antitoxin and an antihistamine drug is given during the first few hours of treatment. Sixty-two patients manifesting intradermal sensitivity were thus treated without occurrence of symptoms suggesting anaphylactoid shock. Penicillin should be given intramuscularly. The authors suggest 1,200,000 units of benzathine penicillin G (Bicillin), which will provide an effective blood level over a period of several days and obviate the necessity of further disturbing the patient. If the infected area can be identified it should be debrided. Management of the stage of symptomatic treatment includes measures to lessen excitability and the tendency to tetanic spasms and convulsive seizures, measures to counteract respiratory difficulty, and good supportive treatment and nursing care (details are given). In experimental animals with tetanus the authors were unable to demonstrate any efficacy of cortisone. In none of five patients studied was there a detectable level of tetanus antitoxin either before or at two to four weeks after a single dose of tetanus toxoid. These results suggest that ordinarily little or no active immunity develops as a result of clinical tetanus, and it is, therefore, implied that patients with tetanus should have an active immunization program after recovery.

Canadian Medical Association Journal, Montreal

Abstracted by H. M. Keith, M.D.

78, No. 3 (Feb. 1) 1958

* The Rising Incidence of Scurvy in Infants: A Challenge to the Physician and the Community. W. S. Whelen, D. Fraser, Elizabeth C. Robertson, and Hedy Tomczak.—p. 177.
* Clinical Experience with a Newer Non-Mercurial Oral Diuretic—Rolicton.—J. Wener, R. Friedman, and R. Schucher.—p. 200.
Phenoxymethyl Penicillin (Penicillin V) in the Treatment of Streptococcal Tonsillitis. P. K. Fraser.—p. 186.
Transfusion of Girls and Women Can Kill Their Babies. Bruce Chown.—p. 208.
The Physiological Basis for Supplemental Oxygen in the Newborn. P. R. Swyer.—p. 236.
The Place of Early Induction in the Management of Erythroblastosis Fetalis. B. Chown.—p. 252.

The Rising Incidence of Scurvy in Infants: A Challenge to the Physician and the Community.—Infantile scurvy has been a rare disease in recent years. However, 79 cases of acute scurvy were seen in Toronto in five years (46 in one year). It is concluded that, parental claims to the contrary, an inadequate intake of vitamin C was, of course, the

etiologic factor. The authors emphasize the administration of orange juice in sufficient quantity, rather than the multiple vitamin preparations. They also demonstrate that methods of preparing the orange juice (fresh, canned, frozen) make no significant difference in the content of vitamin C. Even boiling the juice for 40 minutes in an open saucepan destroyed only 15% to 25% of the vitamin C.

Clinical Experience with a Newer Non-Mercurial Oral Diuretic—Rolicton.—Rolicton is an aminouracil compound, synthesized by Papesch and Schroeder, and is a diuretic whose action is that of inhibition of reabsorption of sodium ions by the renal tubule. Twenty patients with congestive failure were treated for periods up to 11 months. No significant changes in serum sodium chloride, potassium, or CO_2-combining power were observed. Three to six 400 mg. tablets of Rolicton were given daily (adults). Rolicton seems to be a safe and well-tolerated oral diuretic and, in the cases reported, was useful in maintaining the edema-free state. However, added mercurial injections were usually required to initiate the diuresis.

Circulation, New York

Abstracted by Anthony C. Nolke, M.D.

17, No. 1 (Jan.) 1958

* Endocardial Fibroelastosis: Angiocardiographic Studies. Leonard M. Linde, Forrest H. Adams, and Bernard J. O'Loughlin.—p. 40.

* Congenital Malformations of the Heart Associated with Splenic Agenesis: With a Report of Five Cases. Enid F. Gilbert, Kinsuke Nishimura, and Bernice G. Wedum.—p. 72.

Patent Ductus Arteriosus in Association with Pulmonic Stenosis: A Report of Six Cases with Additional Noncardiac Congenital Anomalies. Douglas C. Heiner, and Alexander S. Nadas.—p. 232.

Corrected Transposition of the Great Vessels, Atrioventricular Heart Block and Ventricular Septal Defect: A Clinical Triad. Weldon J. Walker, Denton A. Cooley, Dan G. McNamara, and Robert H. Moser.—p. 249.

Dextrocardia with Pulmonary Stenosis and Functionally Single Right Ventricle. Joseph Fisher and Soon Kyu Suh.—p. 266.

Endocardial Fibroelastosis: Angiocardiographic Studies.—The authors recognize endocardial fibroelastosis as a cause of severe cardiac hypertrophy in infants.

The report describes an angiocardiographic sign which may be an aid in the diagnosis of the disease. Four children were studied in whom the chronic form of primary endocardial fibroelastosis was diagnosed clinically. The case histories and pertinent findings were given.

The angiocardiograms in these patients with endocardial fibroelastosis uniformly showed prolonged retention of dye in an enlarged left ventricle.

It was pointed out by the authors that similar studies on other rare cardiac conditions, such as glycogen-storage disease of the heart, aberrant left coronary artery disease, and idiopathic myocarditis, must be done before any specificity of this sign can be evaluated.

Congenital Malformations of the Heart Associated with Splenic Agenesis: With a Report of Five Cases.—The authors describe congenital absence of the spleen as almost invariably associated with severe cardiac anomalies. The authors review the literature on this subject and also present five additional cases.

Splenic agenesis was found to be associated with anatomic malformations of the heart that included variations in systemic and pulmonary return; defects in the atrial and ventricular septa; anomalies of the truncus, pulmonary artery, and valve, and atrioventricular orifice. Dextrocardia and anomalies of the abdominal viscera and lungs, resulting in bilateral symmetry or partial situs inversus, were also frequently reported.

The authors review the previously reported 81 cases from the literature and chart the details of sex, age of patient, and character of the lesions.

Embryonic theories and features pertinent to the discussion are described.

The case histories of their five additional cases are given.

The current theories in etiology of congenital malformations associated with splenic agenesis are discussed. The authors advance the proposal that a lethal factor, possibly the product of a faulty ovulation, specifically affects the germinal bed of the mesoblastic surface of the celom at an ovulatory age of 24 to 28 days.

Medical Journal of Australia, Sydney

Abstracted by George H. Lowrey, M.D.

2, No. 14 (Oct. 5) 1957

Anaesthetic and Allied Considerations in Relation to Children's Orthopaedic Operations. W. H. J. Cole.—p. 498.

2, No. 16 (Oct. 19) 1957

The Mole Technique for Dilatation of Oesophageal Strictures. L. P. Gray.—p. 573.

2, No. 17 (Oct. 26) 1957

Illness in Twins: I. A Study of Twins from a General Hospital Population. R. K. Doig and F. Pitman.—p. 612.
Illness In Twins: II. Duodenal Ulcer. R. K. Doig.—p. 617.
Obliterative Arterial Disease in a Young Girl. L. P. Wait.—p. 621.
Child Health and Psychiatry in China Today.—p. 630.

2, No. 18 (Nov. 2) 1957

Some Recent Concepts of the Physiology of the Cerebro-Spinal Fluid. R. D. K. Reye.—p. 637.
Hydrocephalus in Childhood. Alan Williams.—p. 639.
Hydrocephalus in Infancy: Clinical Features, Diagnosis and Treatment. M. Sofer Schreiber.—p. 640.
A Goitrogenic Factor in Milk. F. W. Clements.—p. 645.
Problems of Children in a Long-Stay Hospital. Douglas Galbraith.—p. 646.
The Changing Face of Osteomyelitis in Children. David L. Dey.—p. 648.
* Hyponatraemia and Central Nervous System Disease. Donald B. Cheek.—p. 649.
The Handicapped Child.—p. 653.
Proceedings of the Australian Paediatric Association.—p. 661.

2, No. 19 (Nov. 9) 1957

* Staphylococcal Pneumonia in Infancy and Childhood. J. D. Harley.—p. 673.
Cystic Disease of the Lungs in Childhood. J. M. Alexander.—p. 676.
Reading Disorders in Childhood. Elizabeth A. Kemp.—p. 678.
The Management of Double Ureters in Children. F. D. Stephens.—p. 679.
* Palmar Pulsation: A Physical Sign of Patent Ductus Arteriosus in Infancy. Douglas Stuckey.—p. 681.
The Pierre Robin Syndrome. J. Steigrad.—p. 682.
Congenital Ducto-Pulmonary Atresia: A Variant of Pulmonary Atresia of Some Clinical Importance. M. L. Powell and H. G. Hiller.—p. 684.
Hepatitis in Infancy. Felix Arden.—p. 683.
Acute Haemolytic Anaemia Associated with Acute Glomerulonephritis in Infancy. S. E. J. Robertson.—p. 686.
Ectopic Ureter. Edward S. Stuckey.—p. 688.
A Diencephalic Syndrome of Early Infancy. Lorimer Dods.—p. 689.

Hyponatraemia and Central Nervous System Disease.—Several conditions involving the central nervous system will produce changes in the extracellular and intracellular electrolyte balances. Commonly in tuberculous meningitis there is an associated metabolic alkalosis with a lowered sodium and chloride concentration in the blood. In these patients the use of a reliable technique for estimation of extracellular volume shows that this parameter is increased, and the total body chloride content is found to be normal or increased. The alteration in chemical composition is referred to as "hypotonic expansion of the extracellular fluid." The author warns that, since metabolic alkalosis leads to a loss of potassium through the kidney, care must be taken to avoid severe sodium loading. It is possible that the lowering of spinal fluid chloride in tuberculous meningitis is explained on this principle. This finding has been known for a long time by the clinician. The author emphasizes that in encephalitis and other types of meningitis hyponatremia and hypochloremia can occur. It is emphasized that the complication of water intoxication can aggravate the low chloride and sodium. In certain lesions of the central nervous system, such as head injury, cerebral vascular accident, or tumor of the fourth ventricle, excessive salt excretion may occur. However, in these conditions there is dehydration, hemoconcentration, and other evidence of dehydration.

Staphylococcal Pneumonia in Infancy and Childhood.—This study includes 32 children over a two-year period, 1955 to 1956. The proof of etiology in the majority of these cases was made by culture of pleura aspiration or lung puncture. Twelve of the children were less than 3 months of age, and 19, less than 6 months of age, while only 4 were beyond 2 years. Many of the infants in the first three months had had a history of abnormal delivery, low birth weight, or poor development. Obvious signs of pneumonia followed an eight-day period of signs and symptoms of upper respiratory tract infection in the average case. Approximately one-third of the patients had effusion or other evidence of fluid in the chest cavity. Twenty-two

of the thirty-two cases had radiologic evidence of pulmonary abnormalities, the commonest being consolidation. The signs and symptoms of the pneumonia were not particularly remarkable, except that there was a high incidence of severe toxicity. The author comments that it is probably wise to use combinations of at least two antibiotics to combat this infection, and he believes that the combination of erythromycin and chloramphenicol is most satisfactory. He concludes that in any infant less than 2 years old with signs of localized pneumonia treatment should be instigated as though this was a staphylococcal infection.

Palmar Pulsation: A Physical Sign of Patent Ductus Arteriosus in Infancy.—The author describes the finding of pulsation of the superficial palmar arch as it crosses the heads of the metacarpals in patients with a patent ductus arteriosus. In average cases the pulsation was strong and could be easily felt in the palm of the hand. In a control series of 102 patients the pulsation was absent in 84. The sign became commoner in the older age group but was very uncommon under 2 years of age. In 22 patients with patent ductus arteriosus the palmar pulsation was absent in only 1. The author mentioned that this may be a valuable sign indicating patent ductus arteriosus in the young child.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

53, No. 7 (Feb. 14) 1958

* Chlorpromazine in Poliomyelitic Respiratory Paralysis. Rolf Humbert.—p. 265.

Chlorpromazine in Poliomyelitic Respiratory Paralysis.—In seven cases of respiratory paralysis due to poliomyelitis chlorpromazine was given for sedation. Three of the patients were less than 15 years of age. The patients were receiving artificial respiration. With the exception of a 12-year-old girl, untoward side-effects were noted, particularly a tachycardia. Th use of chlorpromazine in such cases is not recommended, and if it is given special caution is to be observed.

Monatsschrift für Kinderheilkunde, Berlin

Abstracted by Hans Hartenstein, M.D.

105:281-320 (Aug.) 1957

Genesis, Recognition and Treatment of the Anemias of Childhood. Heinz Weicker.—p. 281.
Prophylaxis of Dyspepsia in Young Infants with Arobon. Uwe Stave.—p. 287.
"Lisping" (Sigmatismus Interdentalis): Cause and Treatment. Horst Hartmann and Max Heinrich.—p. 289.
* Biochemical Complications Following Uretero-Sigmoidostomy for Congenital Exstrophy of the Bladder. E. Sieber.—p. 293.
Electroencephalography and Disturbances of the Vegetative Regulatory Nervous System in Childhood. H. Fritzsche and J. Fritzsche.—p. 296.
Testicular Feminization. Erwin Keyser.—p. 302.
Renal Vein Thrombosis in Infants. R. Schutz.—p. 305.
Fenestrae Parietalis Symmetricae (Foramina Parietale Permagna). Hans Rudolf Wiedemann.—p. 310.
Review Article: Pharmacology and Toxicology of Illnesses Due to External Factors. Heinrich Wiesener.—p. 312.

105:321-360 (Sept.) 1957

* Results of the Treatment of Congenital Syphylis with Oral Penicillin. Hans Cailloud and Rudolf Weller.—p. 321.
Variations in the Level of Physiological Icterus of the Newborn Infant. Wolfgang Thoenes.—p. 323.
Late Cerebral Damage Following Icterus Gravis. L. Ballowitz and G. Fleischhauer.—p. 328.
* Treatment of Cerebral Palsy in Children with Akineton. H. Wallis.—p. 334.
Interstitial Pneumonia of Infants with X-Ray Irradiation. H. Fetzer.—p. 337.
Acute, Acquired Hemolytic Anemia (Lederer Type) with Several Antibodies. G. Aselmann and H. H. Hennemann.—p. 340.
High-Voltage Electrophoretic Urinary Studies in a Child with Wilson's Disease. H. G. Noeller, P. Stelgens, and H. J. Kieser.—p. 343.
The Use of Bank Blood in a Closed System in Pediatrics. O. H. Braun and H. Plueckthun.—p. 346.
Review Article: Nutrition and Nutritional Disturbances in Infancy. K. Betke.—p. 351.

Biochemical Complications Following Uretero-Sigmoidostomy for Congenital Exstrophy of the Bladder.—Of 22 children who underwent ureterosigmoidostomy because of congenital exstrophy of the bladder, 21 showed hyperchloremia when examined one year after surgery. Eighteen children also had acidosis; five, azotemia, and two, rickets-like skeletal changes. These biochemical changes could easily be corrected by administration of sodium, adhering to a low-albumen salt-free diet, and frequent bowel evacuation.

Results of the Treatment of Congenital Syphylis with Oral Penicillin.—Between September, 1948, and August, 1955, a total of 95 infants with congenital syphilis were treated at the University of Munich Children's Clinic in Germany. Treatment consisted of 100,000 units of aqueous penicillin G per kilogram per day by mouth for 14 days, divided into eight doses per 24 hours. Thirty patients were followed for five years and twenty-three, for three years.

Clinically, patients improved rapidly; serologic tests became negative after three to four months. No osseous changes were noted radiologically after one year. About one-third of the patients had Herxheimer reactions, with fever (temperature up to 38.5 to 40.0 [101 to 104 F]); none of the reactions was considered as serious. Follow-up studies revealed neither clinical nor serological signs of active or latent syphilis. Mortality was 5%.

Treatment of Cerebral Palsy with Akineton.—Of 14 children with cerebral palsy, some with severe spasticity, treated with the hydrochloride of Akineton (3-piperidino-1-phenyl-1-bicycloheptenylpropanol-1), results were good in 8 patients. Dosage ranged from 1 to 6 mg. per day. Athetoid movements disappeared in one patient. Reversible untoward side-effects occurred in three patients and consisted of hematuria, bladder tenesmus, and urinary retention. Spasticity of the adductor muscles was most resistant to drug therapy and required orthopedic measures in some patients.

Neue Oesterreichische Zeitschrift für Kinderheilkunde, Vienna

Abstracted by Hermann Vollmer, M.D.

2, No. 4, 1957

The Congenital Adrenogenital Syndrome With and Without Electrolyte Imbalance. H. Rössler and P. Schumacher.—p. 263.
* An Epidemic of Benign Serous Meningitis. I. Taneff and A. Heitoff.—p. 281.
Retentio Testis. R. Jonas.—p. 291.
Thallium Poisoning in a Child. R. Nordman.—p. 297.
* Clinic and Therapy of Bone and Joint Tuberculosis. O. Ruziczka and G. Langer.—p. 301.
Capillaroscopy in Oligophrenias of Childhood. H. Gross.—p. 311.
* Formal and Causal Genesis of Dysostosis Mandibulofacialis. E. Zweymüller and O. Stur.—p. 321.
Experience with Comitiadon (Phenyl-α-Chloracetylurea) in the Treatment of Childhood Epilepsy. C. Groh and C. Zenker.—p. 332.
* Renal Calcium Excretion in Nephropathies of Childhood. A. Rosenkranz.—p. 341.
Symptomatic Treatment of Fever in Childhood. W. Karpinski.—p. 347.

An Epidemic of Benign Serous Meningitis.—An epidemic of serous meningitis occurred in Sofia during the summer of 1954. Ninety cases were observed in the hospital. They were characterized by an acute onset with meningeal symptoms, fever, and vomiting; the spinal fluid was clear or slightly turbid and sterile, with normal protein, sugar, and chlorides and mild to moderate pleocytosis. Virus studies were inconclusive. All children got well within two to five days, and no paralysis occurred. At the same time, 54 paralytic cases of poliomyelitis were observed. They showed a less acute onset, less meningeal symptoms and vomiting, and a higher frequency of sore throats. The authors doubt that their cases of serous meningitis were nonparalytic forms of poliomyelitis but assume that a different virus, probably Coxsackie virus, was responsible for this epidemic. In a similar outbreak of serous meningitis in Plowdiw, Coxsackie virus was isolated.

Clinic and Therapy of Bone and Joint Tuberculosis.—About 48 cases of children with bone and joint tuberculosis are reported. The duration of treatment, prognosis, and end-results have been greatly improved by addition of tuberculostatic agents and surgical intervention to the conventional general treatment. Thirteen children in early stages of the disease were cured by antituberculous drugs alone. In the others, repeated aspiration or surgical removal of caseous or necrotic material in combination with local and systemic administration of chemotherapeutic agents led to satisfactory results.

Formal and Causal Genesis of Dysostosis Mandibulofacialis.—One family with the mother and her three children showing this syndrome is described. Another child with this syndrome but with a negative family history is noteworthy by the occurrence of German measles in the mother during the eighth week of pregnancy.

Renal Calcium Excretion in Nephropathies of Childhood.—Oral administration of 10 mg. of acetazolamide (Diamox) per kilogram in healthy children increases renal calcium excretion through inhibition of tubular reabsorption. In children with renal insufficiency and

hypocalcemia renal calcium excretion is low and not increased by acetazolamide. In children with renal disease but without renal insufficiency renal calcium excretion is low but is increased by acetazolamide.

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

257, No. 23 (Dec. 5) 1957

* The Genetic Mechanism of Idiopathic Hyperlipemia. J. D. Boggs, D. Y. Hsia, R. F. Mais, and J. A. Bigler.—p. 1101.

Acute Urinary Suppression After Ureteral Catheterization: The Pathogenesis of Reflex Anuria. J. H. Sirota and L. Narins.—p. 1111.

Principles Governing the Genesis of Congenital Malformations Induced in Mice by Hypoxia. T. H. Ingalls and F. J. Curley.—p. 1121.

Ineffectiveness of Antihistamine Therapy for Gingival Hyperplasia Due to Diphenylhydantoin Sodium. W. R. Breg and J. P. Falcetti.—p. 1128.

257, No. 25 (Dec. 19) 1957

Glutamic Oxalacetic Transaminase in Serum and Cerebrospinal Fluid of Patients with Cerebrovascular Accidents: Demonstration of a Blood-Cerebrospinal-Fluid Barrier. J. Lieberman, O. Daiber, S. I. Dulkin, O. E. Lobstein, and M. R. Kaplan.—p. 1201.

Investigation of the Relation Between Clinical and Tissue-Culture Response to Chemotherapeutic Agents of Human Cancer. J. C. Wright, J. P. Cobb, S. L. Gumport, F. M. Golomb, and D. Safadi.—p. 1207.

The Medical Expert. G. L. Usdin.—p. 1220.

257, No. 26 (Dec. 26) 1957

* Acquired Toxoplasmosis: Observations on Two Parasitologically Proved Cases Treated with Pyrimethamine and Triple Sulfonamides. D. E. Kayhoe, L. Jacobs, H. K. Beye, and N. B. McCullough.—p. 1247.

A Study of Magnesium Metabolism in Acute Renal Failure Employing a Multichannel Flame Spectrometer. W. E. C. Wacker and B. L. Vallee.—p. 1254.

Asymptomatic Enlargement of the Parotid Glands. J. J. Duggan and E. N. Rothbell.—p. 1262.

Antibiotic Combinations: Antibacterial Action of Plasma after Ingestion of Novobiocin or Penicillin G or Both. W. F. Jones Jr. and M. Finland.—p. 1268.

Developmental Arrest Due to Corticosteroid Intoxication in an Infant with Adrenocortical Virilism. A. N. Drescher and N. B. Talbot.—p. 1280.

258, No. 1 (Jan. 2) 1958

* Prolonged Treatment of Urinary-Tract Infections with Sulfamethoxypyridazine. H. G. Grieble and G. G. Jackson.—p. 1.

258, No. 2 (Jan. 9) 1958

Polonged Cough Suppression. E. H. Townsend Jr.—p. 63.

* Obstructing Subglottic Hemangioma of the Larynx in Infancy: Review of the Literature and Report of a Deceptive Case. P. Doermann, J. Lunseth, and R. H. Segnitz.—p. 68.

Bacteriology of the Lower Respiratory Tract in Health and Chronic Diseases. D. V. Pecora and D. Yegian.—p. 71.

The Nephrotic Syndrome (to be continued). H. A. Derow.—p. 77.

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Drug-Resistant Pathogenic Staphylococci in One Community. W. A. Nolen and H. B. Fleisher.—p. 490.

The Genetic Mechanism of Idiopathic Hyperlipemia.—The authors discuss the general features of idiopathic hyperlipemia, namely: a triad consisting of sporadic attacks of acute abdominal pain, xanthomatous type of skin lesion, and a fasting serum that is milky white. The abdominal attacks may be characterized by extreme tenderness, broad-like rigidity, sometimes collapse, fever, increased neutrophils, and anorexia. They may last one to four days and terminate spontaneously with an abrupt fall of serum lipid levels. The xanthomas usually are soft yellow papules and nodules, commonly located on extensor surfaces of knees and elbows, on buttocks and thighs, and also on trunk, face, and hands. Xanthelasma of eyelids is very rare. Lipemia retenalis may be seen when lipids are very high. Coronary artery disease is frequent, with angina and myocardial infarction.

The authors report a case of a 10-year-old girl who was first seen because of the cutaneous lesions. Her health had been good. Total serum lipids were 2217 mg.; cholesterol, 884 mg.; cholesterol esters, 675 mg.; total fatty acids, 1106 mg.; phospholipid fatty acids, 14 mg.; cholesterol ester fatty acids, 496 mg., and glyceride fatty acids, 500 mg/100 ml. The child was followed in the clinic and a year later was brought in with the complaint of several recent episodes of chest pain followed by loss of consciousness during which she "stiffened out" and was unconscious. Shortly after admission she went into another episode and died.

Autopsy diagnosis was extensive atherosclerosis of the aorta, pulmonary artery, heart valves, and cerebral vessels; obstructive atherosclerosis with acute and chronic myocardial infarction; xanthoma tuberosum; bilateral pulmonary edema with early bronchopneumonia.

In examining the rest of the family it was found that two siblings had the disease, that both parents and two other siblings had the disease, and that both parents and two other siblings had elevation of both total and esterified cholesterols, and they were believed to be heterozygotes. Transmission is thought to be recessive.

This disease is thought to be similar to idiopathic hypercholesterolemia except that, unlike the situation in idiopathic hypercholesteremia, the high lipid level in idiopathic hyperlipemia can be partially controlled by diet and heparin therapy, and this should probably be done in view of the serious prognosis.

The studies of the author demonstrated, as had been found before, that the lipid disturbance is characterized by a high β-lipoprotein. They also found that the α-lipoprotein fraction was markedly depressed. They postulate that the disease may be due to the absence of an enzyme which converts β-lipoprotein (or a specific type of β-lipoprotein) to α-lipoprotein.

Acquired Toxoplasmosis: Observations on Two Parasitologically Proved Cases Treated with Pyrimethamine and Triple Sulfonamides.—The authors report on the second and third cases of acute acquired toxoplasmosis treated with pyrimethamine and triple sulfonamides.

The first patient was a research worker in a toxoplasmosis laboratory who acquired symptoms about seven days after scratching his left fourth finger with infected material, even though he immediately washed off the scratch with 70% ethyl alcohol. Dating from the injury, he developed generalized aching of muscles at 5 days, headache and malaise at 7 days, enlarged lymph node in left axilla at 8 days, fever on 9th day, negative serological tests on 9th day, positive dye test on 11th day, generalized lymphadenopathy on 13th day, petechial lesions of skin on 15th day, hemagglutination test positive on 18th day, and complement-fixation test positive on 20th day. Blood drawn at the time of admission and injected into mice intraperitoneally was found to contain Toxoplasma gondii. The lymph node was removed and also killed the mice with T. gondii. CBC was essentially negative except for a neutrophil count of 83% of 5800 WBC. However, during course of illness he showed between 2% and 25% atypical lymphocytes. Urinalysis and liver-function tests were negative. Initial chest x-ray was negative, but nine days later it revealed a slight infiltrate that cleared in several days. EKG's and EEG's were negative. Electrophoretic pattern of serum protein revealed a reversed A/G ratio by the 11th day of symptoms; all the globulins took part in the increase, especially the γ-globulin. The dye test rose to 1:4096 by the fifth week. Treatment was started on the 15th day after the accident and consisted of 50 mg. of pyrimethamine as a loading dose, followed in 6 hours by 25 mg. and then by 25 mg. daily for 20 days. In addition, he received 1 gm. of triple sulfonamides (equal amounts of sulfadiazine, sulfamerazine, and sulfamethazine) every four hours, maintaining a level between 6.9 to 8.6 mg/100 ml. This was continued for 20 days. Thirty-six hours after start of therapy he became afebrile, and by five days after onset of treatment the lymph nodes had subsided. Two months after discharge he developed malaise, mild sore throat, and coryza and was well in several days. He also developed lymphadenopathy, and his dye test rose to 1:16000. Lymph node biopsy revealed reticulum-cell hyperplasia, but T. gondii was not recovered from mice given injections of the node. His symptoms cleared, and he has remained well.

The second patient was a 48-year-old housewife admitted with a diagnosis of acute leukemia. Four months before admission she had had malaise, weakness, and numbness and tingling in both hands. Photophobia with blurred vision developed in her left eye three months before admission. Fever developed two months before admission, and lymph node enlargement, one month before admission. A WBC was 20,000, with 89% lymphocytes, and was thought to represent leukemia. Physical examination essentially revealed fever, generalized adenopathy, and slightly enlarged liver. There was a retinal lesion in the left eye, consisting of a group of yellow-white raised nodules. There was also some infiltrate into the vitreous. All studies were negative until a dye test was done, and the titer was 1:262000. T. gondii was recovered from mice after inoculation with lymph node. Spinal fluid showed 17 lymphocytes and increased protein. The patient was treated with pyrimethamine and triple sulfonamides for 30 days, with rapid improvement in the adenopathy and the retinal lesion. Sixty-six days after treatment lymph nodes were still positive, although there were no clinical symptoms. This patient also had been taking thyroid because of a previous thyroidectomy. Her requirements for thyroid increased greatly. (In animals myxedema may be associated with toxoplasmosis.) With increased thyroid dosage the peripheral neuropathy and edema cleared.

The authors discuss several features of the disease. They point out the fairly characteristic pathology of lymph nodes, namely, reticulum-cell hyperplasia. They mention the possible connection between toxoplasmosis and hypothyroidism. Fever usually lasts about two or three weeks but occasionally much longer. The altered albumin-globulin ratio of the serum proteins had not been previously reported. They mention the two possible causes of ocular lesions, namely, hypersensitivity (usually associated with high dermal sensitivity) and proliferation of the parasites. The skin test does not become positive until late in the disease. However, neither patient had a positive skin test. Dye test becomes positive first, then the complement-fixation test. Toxoplasma meningoencephalitis is rare in the acute form, but it is serious when it occurs. A mild anemia usually develops.

Pyrimethamine is a folic acid antagonist and can produce pancytopenia, and so one must be careful in its use. After doses of 25 mg. twice a day for two days there are measurable levels in the urine for 11 days. The optimum dose (in animals) is many times that of the safe dose in man. Two workers have reported that folinic acid, given along with the drug, will prevent toxicity in mice and yet be effective. The acute stage responds much better to the combined therapy. In the subacute and chronic form the organisms are encysted and cannot be reached.

Prolonged Treatment of Urinary-Tract Infections with Sulfamethoxypyridazine.—The authors report on the use of sulfamethoxypyridazine (Kynex) in the prolonged treatment of urinary infections. Forty-eight patients were treated, ranging from 2 to 73 years. Complete diagnostic work-up, including pyelograms, was done. At least two pretreatment cultures were obtained, and both species and numbers of micro-organisms were reported. Average duration of treatment was 35½ days, with a minimum of 21 days. Dose was 2.5 gm. to start and 0.5 gm. per day, which maintained a blood level between 5 and 15 mg/100 ml., even in those with reduced renal function.

A total of 87 bacterial strains were recovered from pretreatment cultures, of which 66 were Gram-negative. Fifty-six per cent of the 66 were Escherichia coli or coliform species. Enterococcus was found in 12 of 21 Gram-positive cultures. Two-thirds of 31 E. coli strains were eradicated. Of the rest of the Gram-negative rods more strains persisted or emerged than were eradicated. Only 3 of 11 strains of Aerogenes responded favorably. Enterococci were eradicated from 4, suppressed in 2, persisted in 6, and emerged during or after treatment in 10 cases.

There were 19 patients with an anatomical renal lesion, and only 2 had a single species of bacteria; 3 of 5 patients with a complicating systemic disease had a single strain of bacteria; 22 of 24 patients with nonobstructive urinary tract disease and nonsystemic disease had a single species of bacteria. Eight of ten patients with acute infection responded favorably. Nine of thirty-eight patients with chronic infections responded well. Eighty-five per cent of patients with 100,000 organisms or greater per milliliter of urine had significant pyuria. Using, as criteria, freedom from infection for a minimum of six weeks and less than 100,000 bacteria per milliliter of urine (if not the same species as was originally grown out), only 10 of the 48 patients were bacteriologically cured. All 10 were infected with E. coli. Two of the ten had previously had other antibiotics without help. Four patients who failed to respond to sulfamethoxypyridazine were cured by other agents.

Of 63 patients 4 had reactions severe enough to necessitate discontinuing the drug in the first course, and 1, in second course. The commonest reactions were headache and a diffuse erythematous maculopapular rash. Fever, abdominal pain, and dizziness were encountered. Two of the five patients with reactions were able to tolerate the drug on readministration. Nausea was occasionally encountered. There was some suggestion that minor symptoms occurred during the loading dose. The severe reactions occurred in patients with serum levels between 16 and 19 mg/100 ml., which was higher than the mean for the other patients. On re-administration the symptoms were not related to drug level. Reactions occurred during the first three weeks. On readministration of the drug to those with reactions, symptoms recurred within the first few hours or days.

The authors felt that the lack of effect from antimicrobial agents in most cases was due to the emergence of new and resistant strains. They suggested that perhaps bactericidal agents such as bacitracin, polymyxin, and neomycin would be more effective.

Obstructing Subglottic Hemangioma of the Larynx in Infancy: Review of the Literature and Report of a Deceptive Case.—The authors report a case of obstructing subglottic hemangioma of the larynx in a one-month-old infant. This child was referred to them because of dyspnea and a hoarse cry of two days' duration. Physical examination revealed dyspnea, retractions, cyanosis of the nail bed, and a hemangioma, 2×3 cm., overlying the manubrium. Laryngoscopy was negative. Two days later, increased dyspnea necessitated an endotracheal tube. At this time subglottic narrowing with evidence of mucosal inflammation was seen. A tracheostomy was necessary. The baby died a few days later from obstruction due to a mucous plug. Autopsy revealed a spongy hemangioma in the subglottic area under the mucosa. The authors reviewed the literature and found 14 cases in infants, only 7 of whom were cured. In only one other case besides theirs was the hemangioma not grossly apparent. The subglottic area is the usual location and has a bluish or purplish appearance. The authors feel that the

characteristics of this syndrome are (1) location in subglottic area and (2) a vacillating course with episodes of remission and worsening, the worsening thought to be due to a superimposed inflammatory reaction in mucosa overlying tumor. They feel that laryngotracheobronchitis may be differentiated because of its toxic manifestations, its overt inflammation of pharynx and larynx, and its progressive clearing, without relapsing. Vascular ring, which may also have a vacillating course, may be differentiated by a tracheobronchogram. The authors feel that irradiation may effect a cure; they also feel that one must think of this condition and its clinical features in cases of high tracheal obstruction.

Primary Hyperparathyroidism Associated with Hypomagnesemia.—The authors state that conclusive evidence of a clinical syndrome of magnesium deficiency in man is lacking. They report three patients who, in the course of adenomatous hyperparathyroidism proved by surgery, showed clinical abnormalities which they feel were related to magnesium deficiency. The adult normal value for magnesium is 2.13 ± 0.13 mg/100 ml., determined by the method of Briggs, slightly modified. The normal for children is 1.6 to 2.2 mg/100 ml.

The first case was that of a 32-year-old woman whose symptoms before surgery were those related to her hyperparathyroidism. Starting a week after operation she developed numbness and tingling of hands and feet. Thirteen days postoperatively positive Hoffmann's and Chvostek's signs and hyperactive tendon reflexes were noted. An EKG was abnormal. All electrolytes, including Ca and P, were normal, except for magnesium, which was low. Within 48 hours after administration of magnesium sulfate all symptoms had disappeared. Except for one slight drop below normal the serum magnesium remained normal.

The second case was that of an 8-year-old boy who developed a peculiar generalized nonrhythmical twitching movement involving most of his body. Tendon reflexes were hyperactive. Ca was 18 mg.; phosphorus, 3.2 mg., and magnesium, 0.2 mg/100 ml. He continued these symptoms postoperatively, even though Ca remained normal and was given. Serum magnesium was 0.2 mg. He was given magnesium sulfate (3 gm. of 50%) i. m., and the movements stopped within an hour. The movements recurred several times within the next few days and were always relieved by magnesium sulfate. Serum magnesium level did not get up to normal spontaneously until six weeks postoperatively.

The third case was that of a 37-year-old woman who had generalized hyperreflexia preoperatively despite hypokalemia and hypercalcemia. Magnesium analyses were not performed (though blood was drawn) until after operation, and she had no trouble postoperatively. Preoperative levels were found to be 0.7 and 0.8 mg/100 ml.

Magnesium is estimated to be present in amounts up to 1600 mEq. It is found in relatively large quantities in bone; it functions as a coenzyme; it is a major intracellular cation, and it is important in neuromuscular conduction for both cardiac and skeletal muscle. Magnesium deficiency in animals produces vasodilation, hyperirritability of the central nervous system, cardiac arrhythmia, generalized spasticity, and fatal tonic-clonic convulsions. Several authors have reported cases ascribed to magnesium deficiency manifested by muscular twitching and convulsions. These have been found in severe renal disease, eclampsia, epilepsy, parathyroid deficiency, prolonged administration of magnesium-free intravenous fluids, and alcoholism. However, another author reported 16 cases with low magnesium levels without symptoms. Low magnesium has been reported in diabetic acidosis after treatment, chronic renal disease, osteolytic bone disease, hyperthyroidism, cardiac failure, pancreatitis, and diarrhea.

The authors discuss the little that is known about magnesium metabolism in hyperparathyroidism. Some of the literature is controversial. They believe that parathyroid hormone in excess can promote the excretion of magnesium along with phosphorus, especially since the chief reservoir of magnesium is bone. They suggest that hypomagnesemia should be commoner in hyperparathyroidism. They suggest that in cases with symptoms suggesting tetany, but not responding to calcium, one should think of hypomagnesemia.

Epidemic Infection with Coxsackie Virus Group B, Type 5: 1. Clinical and Epidemiologic Aspects.—The authors report a laboratory and clinical study of an epidemic of aseptic meningitis caused by Coxsackie virus, Group B, Type 5. This epidemic occurred in a prosperous community in Iowa. Sanitation was excellent. The study was conducted in several parts: 1. House-to-house surveys were done in randomly chosen areas; a total of 1500 persons were canvassed by a standard questionnaire. 2. Studies of reported cases (reported by a local physician and studied by one of the investigators) were performed; they included 63 hospitalized and 52 nonhospitalized patients. 3. Specimens of sera, stools, throat washings,

and spinal fluids were collected from reported cases, from all or part of 19 families with one or more illnesses, and from 4 "control" families without illness. 4. Mosquitoes, sewage samples of primary effluent, and city water samples were preserved for virus studies (results not reported); viral culture and serological techniques were the usual accepted ones.

Clinical symptoms varied from very minor ones to aseptic meningitis, requiring hospitalization. With aseptic meningitis, headache, stiff neck, and remitting fever with daily spikes were presenting symptoms. Fever lasted 1 to 16 days, with a median of 7. Nausea and vomiting were common, with repeated episodes of vomiting in the first day or two. Myalgia was present in over one-third, with sore throat less frequent. The total duration of the illness was 2 to 22 days, with a median of 9 days, with no age difference. Physical examination revealed usually only nuchal rigidity and injection of pharynx. Of nonhospitalized patients most had minor illnesses with moderately severe headache, nausea with occasional vomiting, low-grade fever, and mild sore throat. Stiff neck and myalgia were less common. Median duration of minor illness was 4 days, with a range of 2 to 15 days. One hundred twenty-two patients were picked up by the survey with minor illness and with the same symptoms. Other infrequent complaints were dizziness, chest pain, chills, tinnitus, and, occasionally, diarrhea. Laboratory findings were as follows: 43 of 45 spinal fluids of hospitalized patients showed pleocytosis from 0 to 2400, with average of 570; many polymorphonuclear cells were found early, but later most cells were mononuclear; total protein averaged 15 to 90 mg/100 ml., with average of 41 mg. and above 45 mg. in only seven cases; seven patients without nuchal rigidity had pleocytosis; WBC ranged from 4500 to 20,000, with a median of 9000 and 67% below 10,000; differential counts were normal.

The epidemic lasted 12 weeks, with the peak about 7th week and a rapid fall. This was true of both hospitalized and survey cases. Data appeared to indicate an incubation period of three to five days. The over-all attack rate appeared to be 8%. Younger age groups (0 to 9 years) had the highest attack rate. Secondary attack rate in families was 15%. Virus was isolated from stools, throat washings, or cerebrospinal fluid (2 of 19) in 66% of patients with aseptic meningitis, in 61% of patients with minor illness, in 41% of family contacts (contacts without apparent disease), and in 30% of 10 well "control" patients (no cases in family). Virus was present in stools of patients up to 36 days after onset and in throat washings up to 6 days after onset. A fourfold or greater rise in neutralizing antibodies found in 57% of patients with aseptic meningitis, 61% with minor illness, and 27% of family contacts (total number of paired sera was 91). Complete studies on 19 families revealed that 66% of 85 persons submitting specimens had evidence of infection.

The authors felt that there was enough evidence to suggest that the minor illness and aseptic meningitis were caused by the same agent. Their data again bore out the fact that Coxsackie virus infection is more apt to cause aseptic meningitis in the younger group (under 20 years). However, unlike the situation in other epidemics, there were fewer adults with the picture of pleurodynia. They felt that their data showed that spread of the disease was person-to-person contact but could not tell if it were via the oropharynx or the intestinal route.

Immediate Therapy for the Acute Attack of Asthma: A Comparison of Epinephrine and Orally and Intravenously Administered Prednisolone.—The authors emphasize the need for rapid relief in patients with severe wheezing. The marked beneficial effect of the corticosteroids on selected forms of bronchial asthma is known, and the authors feel that a considerable experience with prednisone and prednisolone shows their value in relieving the attack of asthma without the salt-retaining qualities that other compounds have, but they do not produce relief before 6 to 72 hours when given orally. The authors compared the effect of epinephrine (i. m.), prednisolone given orally, and prednisolone given intravenously on patients with severe asthma. The tests were made by measuring vital capacity before medication and at intervals afterward. Results showed that epinephrine gave marked relief within 30 minutes (0.3 to 0.5 ml. of 1:1000 or 0.5 to 1.0 ml. of 1:500 in oil). A single intravenous dose of prednisolone (33.5 mg.) was given. Not much change noted in the first three hours. The same was true after oral administration of a tablet of prednisolone (33.5 mg.). Since the peak plasma level of 17-hydroxycorticosteroids occurs almost immediately after intravenous injection of prednisolone and one to three hours after oral ingestion, and since both routes still take about the same time for the relief of symptoms, it would appear that the plasma level is not the factor determining clinical response.

Mima Polymorpha Meningitis: Report of a Case and Review of the Literature.—The authors report a case of meningitis apparently caused by a rare organism which can easily be confused with the Neisseria group. This organism, Mima polymorpha, was first isolated from patients with urethral discharge and also from normal patients. It has variable morphologic characteristics which mimic other Gram-negative organisms, especially neisserieae. Only a few reports are in the literature about these organisms, which often give rise to errors in bacteriologic diagnosis. Mimeae organisms have been recovered from a variety of human sources: vaginal, urethral, and conjunctival secretions; war wounds; chancroid lesions; urine, ear, and respiratory tract secretions; blood; brain; meninges; spinal fluid; petechiae; bone marrow, and synovial fluid. They have also occasionally been recovered from apparently healthy persons and from river water. Only a few cases of documented disease have been reported—severe and often fatal cases of meningitis, septicemia, and endocarditis.

The case reported is that of a 63-year-old man who presented as having pneumonia. Pneumococcus was grown out of the sputum. However, the patient did not respond to penicillin. He had evidence also of liver disease (jaundice) and urinary disease (elevated nonprotein nitrogen, albuminuria, pyuria). On the ninth day a stiff neck developed. Lumbar puncture revealed a normal spinal fluid except that by the next day a Gram-negative diplococcus, oxidase-positive, grew out of the culture. Repeat lumbar puncture on the next day showed 30 cells, 80% lymphocytes. Gram-negative diplococci, intra- and extracellular, were seen on smear. Blood culture was also positive for the same organism. The patient was given sulfadiazine and hydrocortisone because of toxicity and he rapidly recovered, in spite of the fact that the organism was not sensitive to sulfadiazine. After recovery signs of liver and urinary disease also cleared up. The organism was identified at the Walter Reed Army Institute of Research as M. polymorpha, Type I. Although the spinal fluid findings were not characteristic of meningitis, the isolation twice of the same organism from spinal fluid and also from blood culture suggests that it actually did cause septicemia and meningitis. The dramatic recovery with steroids and sulfadiazine (to which it was not sensitive by the disc method, which, however, is not very reliable for sulfonamide testing) was hard to explain.

In the author's review of the literature, only eight cases were uncovered in which the infections were serious and often fatal. Five cases of meningitis occurred, including one case with Waterhouse-Friderichsen syndrome. Two died, including an infant 1½ years old. Three cases of endocarditis, including an 8-year-old boy, with one death were reported. One case of septicemia with death was reported. Numerous other minor infections, such as conjunctivitis, vaginitis, and therapy-resistant gonorrhea, have grown out of these organisms, but they can be found in the same secretions in normal persons, and so their relationship to these diseases is in doubt.

There are three genera in the tribe Mimeae. They are Mima (M. polymorpha), Herellea (H. vaginicola), and Colloides (C. anoxydana). Morphologically, they are identical pleomorphic Gram-negative organisms, often with some tendency to Gram-positivity. The authors mention briefly some of the cultural characteristics and point out that a precipitin technique is fairly specific for identifying them. In general, these organisms have been sensitive to chlortetracycline and oxytetracycline, somewhat sensitive to chloramphenicol, and usually resistant to the other antibiotics. However, not a great deal of work has been done on this phase.

Pediatrics, Springfield, Ill.
Abstracted by William W. Cleveland, M.D.

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Tolerance of Infants and Children to Fat Administered Intravenously. M. L. Williams and R. Kaye.—p. 809.
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* Surgical Complications of Staphylococcic Pneumonia. J. H. Fisher and O. Swenson.—p. 835.
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Acute Diphenylhydantoin Intoxication: Report of Two Cases. J. H. Moling and James J. Posch.—p. 877.
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Pediatrics and Society: Interpretation to Schoolteachers and Other Professional Persons on Handicapping and Chronic Conditions. S. M. Wishik.—p. 907.
Education: Undergraduate Teaching of Pediatric Rehabilitation. A. Kanof.—p. 910.
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Surgical Complications of Staphylococcic Pneumonia.—A review of the authors' experience with 18 patients manifesting surgical complications of staphylococcic pneumonia is presented; these complications involved emphyema, pneumothorax, fibrothorax, and pneumatoceles. A frequent occurrence of empyema and pneumothorax was noted, and early drainage of the pleural space by one or more catheters inserted intercostally is advised. This management was of course in addition to appropriate antibiotic therapy and with such a program the occurrence of fibrothorax should be rare. When fibrothorax occurs, excision prior to development of deformity of the chest is advised. The finding of pneumatocele in cases of staphylococcic pneumonia was present in over half of the cases, and these were noted to resolve over a period of several months in most cases. In the rare case in which progressive enlargement of cysts occurs and produces symptoms excision of the cyst is recommended.

Pediatriya, Moscow

Abstracted by Moses Grossman, M.D.

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Achievements of Native Pediatrics in Respiratory Diseases in 40 Years. Y. F. Dombrovskaya.—p. 59.
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Forty-Year Study of Physical Development, Health and Morbidity of Children Under Soviet Power.—A. G. Tseitlin.—p. 74.
Activity of Moscow City Children's Hospital No. 2 (1917-1957). V. A. Krushkov.—p. 81.
History of Pediatrics. E. D. Zabludovskaya.—p. 91.

This whole issue is devoted to the 40th anniversary of the Soviet Revolution and the advancements in the field of pediatrics.

35, No. 11 (Nov.) 1957

Problems in Care, Prophylaxis and Treatment of the Newborn. I. A. Shtern.—p. 3.
Measures Against Sepsis in the Newborn. B. N. Moshkov.—p. 12.
Peculiarities of Hemoglobin Metabolism in Sepsis of the Premature Newborn. L. E. Probatova and T. V. Fokina.—p. 18.
Sucking Reflex in the Newborn. L. P. Kuzmenko.—p. 22.
The Influence of Extrauterine Life upon the Development of the Cortex of the Optic Area in Prematures. E. N. Kosmarskaya.—p. 27.
The Qualitative Composition of the Red Blood Cell of the Newborn (Erythrographic Study). I. I. Gitelzon, I. A. Terskov, and E. D. Lukanitcheva.—p. 33.
Nonspecific Antihyaluronidase Activity in the Blood Serum of Healthy Children. M. S. Ignatova.—p. 40.
Bronchogenic Lung Cysts in Children. B. E. Gurevitch.—p. 58.
Sacrococcygeal Teratoma. E. M. Borovay.—p. 73.
Combined Treatment of Hemangiomas of the Integument and Mucous Membranes in Children. N. I. Kondrashin.—p. 77.

35, No. 12 (Dec.) 1957

Achievements in the Field of Rheumatic Fever for 40 years. A. B. Volovik.—p. 3.
Clinical and Pathogenic Peculiarities of Rheumatic Fever in Juveniles. R. A. Kalyuzhnaya.—p. 9.
Comparative Evaluation of Children with Inactive Rheumatic Fever in Urban and Village Schools. A. P. Zveryaev.—p. 21.
Moscow City Children's Clinical Hospital No. 1: Forty Years of Soviet Public Health Activity. E. G. Prokhorovich.—p. 26.

The Experience of Dynamic Control for Physical Development of Children in Moscow Kindergartens. M. I. Korsunskaya.—p. 40.
Pericardial Diverticulum in Early Childhood. I. M. Medzievich.—p. 50.
Hyaluronidase Activity of Human Urine in Different Age Groups. A. Y. Broytman.—p. 58.

36, No. 1 (Jan.) 1958

Correlation of Forms of Infection and Morbidity in Tuberculosis in Early Childhood. S. V. Rachinsky.—p. 7.
* The Effect of Repeated Increased Doses of BCG Vaccine on the Organism of Infants. A. A. Efimova.—p. 14.
Electrocardiographic Studies in Children with Various Forms of Pulmonary Tuberculosis. V. P. Bisyarina.—p. 23.
The Pathogenesis and Clinical Course of Juvenile Tuberculosis. A. O. Gurevich, E. S. Westerman, and A. K. Portsiakhova.—p. 29.
Relapses of Tuberculous Meningitis in Children. V. N. Kritsky.—p. 34.
Preliminary Results of Treatment of Tuberculous Meningitis Without the Subarachnoid Introduction of Streptomycin. K. P. Salganik.—p. 40.
Tuberculosis of the Upper Respiratory Tract in Children. S. I. Agroskin and E. P. Davydovich.—p. 43.
The Clinical and Diagnostic Significance of V. A. Waldman's Cupping Glass Test in Certain Diseases of Children. E. K. Mullerbeck.—p. 60.

Pediatricians in the U. S. S. R.—The development of pediatric education and specialization in the field of pediatrics is reviewed in this paper. At the present time, out of 68 medical schools, 66 have a chair of pediatrics which gives students a medical foundation in pediatrics. In addition, there are 25 pediatric faculties which educate pediatricians. The professorial ranks number 830 persons— 85 of them full professors.

In 1956 there were 40,124 recognized pediatricians in the Soviet Union, compared with 20,298 in 1947 and 11,566 in 1937. There were 2513 graduating pediatricians in 1956, as compared with 2283 in 1947.

Pediatrics in the Soviet Union is now considered one of the four principal clinical disciplines, and there is a shortage in the ranks of pediatric educators. The future development of pediatrics is thought to be along the lines of subspecialization.

Comment (by M. Grossman, M.D.).—Pediatricians as they are seen in the Soviet Union are different from those in the United States. They are students whose medical education has been very heavily slanted toward pediatrics but who have not had the type of postgraduate training that we have in this country.

Moscow City Children's Clinical Hospital No. 1: Forty Years of Soviet Public Health Activity.—In 1957 the first Moscow Children's Hospital had 800 hospital beds, three outpatient departments (one of these for consultations only, which had 15,687 visits), one 75-bed convalescent home for rheumatic fever, and a day hospital which handled 80 children a day. In 1956 the hospital handled 14,171 inpatients, 178 convalescents, and 494 day hospital patients. The population which this hospital serves consists of 20,000 children, including 12 kindergartens and 8 schools.

In 1956 there were 558 diphtheria inpatients, with a mortality of 0.8%. Dysentery incidence per 1000 children in 1956 was 3.2 as compared with 145 in 1925 and 20 in 1950; poliomyelitis, 416 in 1956; rheumatic fever cases per 1000 were 28 in 1956, of which 0.7% had their first attack. Pneumonia was responsible for 12% to 13% of all admissions, and the mortality was appreciable only in the first year of life.

Surgical cases accounted for 22% to 23% of admissions, or a total of 3500 in 1956. Of these, 30% were for trauma; 16%, appendicitis; over-all surgical mortality was 1.3%.

The Effect of Repeated Increased Doses of BCG Vaccine on the Organism of Infants.—The author found that BCG vaccination, with use of Kolman's method, gives only 30.3% positive tuberculin tests by six months and only 44.2% by the end of one year. This led her to investigate further different methods of BCG vaccination, and this is a report on the use of method proposed by De Assis.

A series of six oral vaccinations (starting with a dose of 60 mg. and adding 60 mg. to each successive vaccination by mouth, at intervals of one month) was tried in 317 children, from 1 month to 3 years of age, with initial positive and negative tuberculin tests, and proved the innocuousness of this method. The above regimen can be carried out along with other prophylactic vaccinations.

In this method of vaccination the intensity of tuberculin allergy has a tendency to increase. At the end of these repeated vaccinations the postvaccinal allergy reached almost 100%.

This method of vaccination does not produce any desensitizing effect. The criterion of infection, apparently, is the pronounced tuberculin allergy, which should be attained by increase of the oral dose of vaccine and by multiple vaccinations, in accordance with individual properties of a child in developing allergy. Usually two or three vaccinations will suffice.

Vaccination of children infected with tuberculosis is not expedient.

Presse médicale, Paris

Abstracted by R. Le Dentu, M.D.

66, No. 18 (March 5) 1958

* Action of Chlorpromazine on the Infant's Electroencephalogram. P. Laget, R. Laplane, and R. Salbreux.—p. 395.

Action of Chlorpromazine on the Infant's Electroencephalogram.—The authors studied the effects of chlorpromazine on the electroencephalogram of 30 normal infants aged from 15 days to 2½ years. The product was administered either orally or intramuscularly in the dosage usually employed in therapeutics (2 to 5 mg. per kilogram of body weight per day during several days for the oral route and 1 to 5 mg. per kilogram for the intramuscular route) one and one-half hours prior to the taking of the EEG.

The recording was made with a 10-derivations device; the activation test, by means of intermittent luminous stimulation, was performed on each of the infants for the control tracing as well as for the tracing effected under chlorpromazine.

In one-third of the cases, whatever the age of the infant or the route of administration of chlorpromazine, there was no alteration in the waking or sleep tracing. In the remaining two-thirds (20 cases) the product promoted very slight alterations in the waking tracing: In 5 cases there was a slight flattening; in 15 cases, a moderate slowing and increase in voltage of the basic rhythm. The sleep tracing, however, usually presented no modification or merely a slight diminution in the voltage of the slow elements.

In those cases where some alterations in the waking tracing did occur these were ascribed to variations in the consciousness level (depression in watchfulness, presomnolence). In no case did chlorpromazine cause abnormal graphoelements to appear. The authors compare these observations with the experimental data on animals and ascribe the action of the drug to its depressive effect on the activating reticular formation.

The drug consequently seems to be very useful in infantile electroencephalography with a view to inducing a physiologic sleep with no overcharge of tracing by parasite graphoelements.

News and Comment

ANNOUNCEMENTS

Institute in the Care of Premature Infants.—In the fall of 1958, the Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their 10th year of operation. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and consultants in state and local premature programs. The attendance at each institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses, of four weeks' duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1958-1959 year are definitely scheduled to start on the following dates: Sept. 22, 1958; Nov. 3, 1958; Jan. 12, 1959; Feb. 23, 1959, and April 20, 1959. Early application for these institutes is essential, since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 E. 68th St., New York 21.

GENERAL NEWS

American Heart Association Names Three Scientists for Lifetime Posts in Basic Research.—The American Heart Association has announced the appointment of three Career Investigators, bringing to six the number of scientists whose research is being supported on a lifetime basis by the Association and its affiliates.

The new Career Investigators are Dr. David B. Sprinson, Professor of Biochemistry, Columbia University College of Physicians and Surgeons; Dr. John V. Taggart, Professor of Medicine, also at Columbia; Dr. Lewis W. Wannamaker, Associate Professor of Pediatrics, University of Minnesota Medical School.

Already working as Career Investigators are Dr. Victor Lorber, University of Minnesota, appointed in 1951, and Drs. John R. Pappenheimer and Albert H. Coons, both of Harvard Medical School and both named in 1953.

The Career Investigatorship is a form of award pioneered by the American Heart Association in order to foster unrestricted research on a lifetime basis by outstanding scientists. Providing $30,000 per year to cover the Career Investigator's salary and help underwrite the expenses of his laboratory, it relieves the recipient of pressures arising from short-term forms of support or the need to supplement his income through teaching or other nonresearch activity. Under the terms of the award, the Career Investigator is free to pursue his ideas wherever they may lead. He may work at any institution he selects, and he is not obliged to report or publish except when he feels justified in doing so.

The three men named are concerned with various aspects of basic research, studies aimed at filling gaps in underlying knowledge of bodily processes. Through such studies, it is felt, new light will be shed on the functioning of the heart and circulatory system, although direct application to specific disease problems is not now involved.

Dr. Sprinson.—Dr. Sprinson, 48, is working in the general field of intermediary metabolism. In some 15 years of research at Columbia University, Dr. Sprinson has dealt with a number of complex aspects of the body's use of amino acids for the formation of proteins, certain types of fatty materials such as phospholipids, and nucleic acids. He has also worked on the origin of the "benzene ring" of certain natural products.

Dr. Taggart.—Dr. Taggart, 41, is a physiologist and biochemist whose chief sphere of interest is the kidney. The kidney, often called the body's "master chemist," is closely linked to some forms of circulatory disease, notably congestive heart failure and high blood pressure.

Dr. Taggart's kidney studies are focused on the tubules. Dr. Taggart uses the tubule as a tool for studying transport mechanisms, the basic problem of how substances move in and out of cells, across cell walls. His special concern is with the way in which energy arising from the metabolic activity of the cell enters into this process.

Dr. Wannamaker.—Dr. Wannamaker's research is concerned primarily with the way in which streptococcal infections apparently "trigger" rheumatic fever, leading cause of heart disease

among school-age children and young people. He is presently studying the chemical substances or enzymes produced by various strains of streptococci following their invasion of the human body.

From 1948 to 1952, Dr. Wannamaker, now 35, served with the Streptococcal Disease Laboratory at Warren Air Force Base in Wyoming. He was largely responsible for the design and execution of studies carried out there among military personnel through which much new knowledge was gained of the way in which streptococcal infections spread, including the greater risk of rheumatic fever resulting from overcrowding (as in military barracks). The rheumatic-fever-prevention program of the American Heart Association and its affiliates is based, in part, on the data collected through the investigations at the Wyoming base.

New Awards.—The awards to the new Career Investigators became effective July 1, 1958. They bring to 186 the number of individual awards announced by the Association and its affiliates for the forthcoming fiscal year, or a commitment of $1,523,000. Other 1958-1959 fellowship awards include 84 Established Investigatorships, providing five years of uninterrupted support to mature scientists conducting independent programs of research; 62 Research Fellowships, and 34 Advanced Research Fellowships. Given usually for two years, the latter two categories enable young scientists to obtain training in research methods under experienced guidance.

In addition, the Association will soon announce a large group of awards in its Grants-in-Aid category for 1958-1959, while affilitated heart associations will make substantial awards of their own to scientists both in their areas and throughout the country. In all, the American Heart Association and its affiliates have channeled more than $31,000,000 into support of research since 1948, when the Association was reorganized as a voluntary health agency.

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Atlantic City, N. J., May 3, 4, and 5, 1958.

Adams, E. Wade, Fort Wayne, Ind.
Alexander, John Wesley, Orange, N. J.
Antonacci, Dominic J., San Francisco.
Beatman, Bernard, New London, Conn.
Bookmyer, Robert M., Birmingham, Mich.
Bregman, Robert L., Alexandria, Va.
Bridgers, John David, Philadelphia.
Budnick, Irwin S., Margate City, N. J.
Carper, John M., Lancaster, Pa.
Carr, Robert Lon, Lubbock, Texas.
Castellano, Philip J., Jackson Heights, N. Y.
Chadwick, David Lee, Los Angeles.
Chemris, Walter Mark, Paramus, N. J.
Chicoine, F. Luc, Montreal, Canada.
Chusid, Emanuel, Mt. Vernon, N. Y.
Cochran, Gloria Grimes, Silver Spring, Md.
Cooperman, Selma S., Long Beach, Calif.
D'Adesky, Raymond G., Marquette, Mich.
Danufsky, Philip G., Hillside, N. J.
De Asmar, Neida Nunez, Santurce, P. R.
DeMuth, George R., Ann Arbor, Mich.
DiCosimo, Charles J., Syracuse, N. Y.
Ebin, Eva V., Forest Hills, N. Y.
Ferazzi, Patrick S., Battle Creek, Mich.
Fidler, William L., III, Cranford, N. J.
Findaro, Joseph T., Woodside, N. Y.
Fitzhugh, A. Stuart, Jr., Griffin, Ga.
Giardino, Joseph P., Gloversville, N. Y.
Goldstein, Raphael, Buffalo, N. Y.
Graham, George G., Cleveland.
Hamburger, Robert N., Milford, Conn.
Hansell, Howard W., Wyncote, Pa.
Huleatt, Thomas R., Hartford, Conn.
Jaros, Alice, Hartford, Conn.
Jones, Elizabeth C., Evanston, Ill.
Karowe, Harris E., Waltham, Mass.
Katz, Samuel L., Boston.
Kessler, Sheldon, Mt. Vernon, N. Y.
Kowlessar, Muriel C., Brooklyn, N. Y.
Kramer, Irving, Baltimore.
Lathrop, Frederic W., Jr., Plainfield, N. J.
LaVeck, Gerald D., Buckley, Wash.
Levinthal, Jeana D., Brookline, Mass.
Lisbin, Arthur D., Los Angeles.
Lombardo, Thomas A., Buffalo.
Lorincz, Andrew E., Chicago.
Lubow, Henry, Miami Beach, Fla.
McArthur, James A., Salinas, Calif.
McKusick, Marjorie Jane, Wilmington, Del.
Menashe, Victor D., Portland, Ore.
Millichap, Joseph G., Bronxville, N. Y.
Mortati, Saverio G., Yonkers, N. Y.
Nigro, Anthony, Reading, Mass.
Overton, Thomas P., Richmond, Va.
Palladino, Neil M., Plainview, Long Island, N. Y.
Pearlman, Ira W., Chevy Chase, Md.
Reiman, Reuben H., Forest Hills, N. Y.
Rosenbaum, Sidney A., Arlington, Va.
St. Laurent, P. Guy, Montreal, P. Q., Canada
Scaglione, Carolyn D., New York.
Scaglione, Peter R., New York.

Smith, Lendon H., Portland, Ore.
Spielsinger, David, Patchogue, Long Island, N. Y.
Stallings, James, H., Jr., Arlington, Va.
Thomas, Patricia Zeis, Iowa City.
Tkacz, Charles, Westbury, N. Y.
Watkins, Elizabeth B., New York.
Wheeler, James E., Newton Square, Pa.

SOCIETY NEWS

American Pediatric Society.—There follows a list of officers and members elected to the American Pediatric Society at its annual meeting held at the Hotel Traymore, Atlantic City, N. J., on May 8 and 9, 1958. Officers: Joseph Stokes Jr., President; William L. Bradford, Vice-President; Aims C. McGuinness, Secretary-Treasurer; Robert J. McKay, Recorder (Editor); William M. Wallace, Member of Council (for 7 years). Members: Lewis A. Barness, Philadelphia; Merl J. Carson, Los Angeles; Barton Childs, Baltimore; E. Perry Crump, Nashville, Tenn.; Harriet M. Felton, Galveston, Texas; C. Henry Kempe, Denver; Saul Krugman, New York; Jack Metcoff, Chicago; Samuel Spector, Cleveland; Harry A. Waisman, Madison, Wis.; Reginald A. Wilson, Vancouver, B. C., Canada.

The 1959 meetings of the American Pediatric Society and the Society for Pediatric Research will be held at The Inn, Buck Hill Falls, Pa., on the following dates: The American Pediatric Society starting Wednesday evening, May 6, and concluding with the morning session on Friday, May 8. The Society for Pediatric Research starting Friday afternoon, May 8, and concluding with the afternoon session on Saturday, May 9.

The Society for Pediatric Research.—At the spring meeting of the Society for Pediatric Research held in Atlantic City, N. J., May 6 and 7, the following officers were elected: President, Dr. Sydney S. Gellis, Boston; Vice-President, Dr. Margaret Smith, New York; Secretary-Treasurer, Dr. Clark West, Cincinnati; Council Members, Drs. Irving Schulman, New York, and Alfred Bongiovanni, Philadelphia.

The following physicians were elected to membership: Franklin C. Behrle, Kansas; Robert Brent, Jefferson; Audrey K. Brown, Wayne; James J. Chisolm Jr., Hopkins; Henry G. Cramblett, Iowa; Murray Davidson, Cornell; Murdina M. Desmond, Baylor; Angelo M. DiGeorge, Temple; Frank T. Falkner, Louisville; Angella D. Ferguson, Howard; Richard E. Fowler, Louisiana; Sidney Friedman, Pennsylvania; A. Leonard Luhby, New York Medical College; Leroy W. Matthews, Western Reserve; Charles V. Pryles, Boston; Abraham M. Rudolph, Harvard; Sydney Segal, British Columbia; Phillip Sturgeon, Southern California; Roebrt L. Vernier, Minnesota; William Zinkham, Hopkins.

Books

BOOK REVIEWS

Enuresis: A Clinical and Genetic Study (Supp. 114, Vol. 32, of *Acta psychiatrica et neurologica scandinavica*).—By Bertil Hallgren, M.D. Price, not given. Pp. 159. Ejnar Munksgaards Forlag, Norregade 6, Copenhagen, 1957.

This monograph, published as a supplement to *Acta psychiatrica et neurologica scandinavica*, is a carefully written well-organized cautiously presented study of the clinical aspects of enuresis among 229 subjects from two children's psychiatric clinics in Stockholm. Additional data from 173 affected and 530 unaffected members of the same families are included. The author recognizes the lack of random selection in his material.

Some of the carefully worded conclusions which are derived from statistical treatment of the data are confirmations of common clinical experience—that enuresis endures longer in boys than in girls and among those who have never been dry than among those who regress, that heavy sleep is often associated with enuresis, that emotional problems and regressive behavior are more prevalent in the enuretic than the nonenuretic child, and that unfavorable environment may precipitate the symptom by undermining the child's emotional security.

Other conclusions are less widely known or accepted—that there is a positive association between enuresis and pyloric stenosis, that encopresis is associated significantly with diurnal enuresis, and that physical factors play a minor role in the etiology of the symptom.

The genetic analysis concludes that two types of enuresis probably exist, i.e., a genetically determined nucleus and a nongenetic residue of cases. Attempts are made to fit the data for the genetically determined nucleus to several theories of transmission. It is concluded that inheritance probably depends either upon the activity of a dominant major gene which must be modified by polygenes and the external environment or that polygenes and environment alone are responsible.

No discussion of therapy or of psychodynamic formulations is included.

F. H. Wright

The Good Housekeeping Book of Baby and Child Care. By L. Emmett Holt Jr., M.D. Price, $4.95. Pp. 288, with more than 100 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

As the title implies, this is a book for parents. The eminence of the author in the pediatric world is a guarantee of a superior product. Simplicity and forthrightness characterize the presentation of material. Excess wordage and dogmatic viewpoints are avoided. Facts consistent with modern concepts of child raising are set forth in a manner easy for the parent to grasp, and numerous subheadings permit ready location of desired items of specific information. A generous supply of appropriate illustrations enhances the over-all readability of the book. It deserves a rating of excellent, and physicians can recommend it to their patients confident that the information obtained from it will be accurate, helpful, and up to date.

Lee Forrest Hill, M.D.

Ciba Foundation Colloquia on Endocrinology: Vol. X. Regulation and Mode of Action of Thyroid Hormones. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $8.50. Pp. 307, with 114 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

This volume summarizes present concepts of the regulation and mode of action of thyroid hormones in 18 papers of international origin. There is supplementing discussion of each paper, and there are three general discussions, which provide invaluable perspective and criticism. Although not a clinical volume, it belongs in the library of all whose interest in clinical thyroid physiology is more than casual.

The first eight papers take up hypothalamus-pituitary-thyroid relationships with respect to TSH, iodine metabolism, and thyroid hormone synthesis. Brown-Grant provides an intriguing feed-back hypothesis which assigns to the hypothalamus the role of regulating the content of thyroxin in the blood reaching the anterior pituitary.

The second half of the colloquium is devoted chiefly to the search for the elusive peripherally active forms of thyroid hormones. Mme. Thibault presents provocative evidence that thyroid hormones may be transformed by tissues into several "active derivatives, each of them being specific of a particular function." The last paper ably discusses a neglected area of thyroid research, the influence of the thyroid gland upon immune responses of different species to bacterial infection.

Foundations of Nutrition. By Clara Mae Taylor, Grace Macleod, and Mary Swartz Rose. Fifth edition. Price, not given. Pp. 620, with 128 illustrations and 26 tables. The Macmillan Company, 60 5th Ave., New York 11, 1956.

The new edition of this classic textbook, "Foundations in Nutrition," maintains its previous standards, and, in my opinion, it would be helpful to anyone seriously interested in the field of nutrition. It could well be used in college courses as well as in the teaching of medical students and nurses. It is written lucidly and is well illustrated. It purposely does not attempt to go into the biochemistry of nutrition but gives historical background data interwoven with references to original material. These references are listed at the end of each chapter and include some material as recent as 1956. The appendix is as valuable as the book itself, as it contains tables listing the most important nutritive values of the most commonly used foods on the basis of weight and similar tables listing the same nutritive values of foods in terms of shares of each nutrient per 100 calories of that food. Also included are height and weight tables for infants and children and energy requirements for different ages and sexes. Recommendations in the tables are based on recommendation of the Food and Nutritional board of the National Research Council (1953). The chapters on the feeding of infants and preschool and school-age children are short but informative. The chapters on nutrition and feeding are best taken in reference to the previous chapters, which deal with specific nutrients in detail. The chapter on energy and its determination by colorimetry is one of the most interesting and informative; the data used were compiled from the personal experience of the authors in the experimental laboratories at Columbia University. Further chapters deal with water; protein; minerals, including the trace elements, and the various vitamins. The authors include classical diets constructed to meet varying needs, such as those of pregnant women and growing children. Family diets are constructed with use of common foods, with costs of foods for low-, medium-, and upper-income groups being considered.

The book is highly recommended to anyone desiring a thorough grounding in foundations of nutrition.

ROBERT L. JACKSON, M.D.

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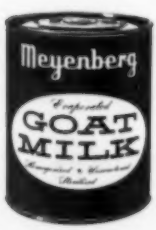

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** Ibid.

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